

THE ETIOLOGY AND PATHOGENESIS OF SOLITARY

ULCER OF THE DUODENUM.

by

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With photographs and 10 Microscopical
Slides of Ulcers.

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THE ETIOLOGY AND PATHOGENESIS OF SOLITARY

ULCER OF THE DUODENUM.

As the subject for my Edinburgh M.D. thesis I propose to take "The Etiology and Pathogenesis of Duodenal Ulcer", and especially deal with that most interesting and obscure form known as the "Solitary peptic ulcer of the Duodenum". The subject of duodenal ulcer at the present moment is often referred to in current medical literature, and although in its beginning a purely medical subject, like gastric ulceration, yet it is to the surgeon that we owe the diagnosis in the great majority of cases, for as a rule, the condition is either diagnosed at a laparotomy for septic peritonitis, or else at an exploratory coeliotomy for some obscure gastric disorder which proves to be secondary to an ulcer of the duodenum.

Collin in "L'ulcere simple du duodenum" These de Paris 1894, could only collect 26 cases in the literature of the previous 10 years. In the Lancet of 1890 I can only find 6 cases given in full, and a record of 51 cases given on 30th June 1900; whilst during/

during November and December 1903 in the Lancet alone no less than 33 cases of duodenal ulceration are referred to, and all by surgeons, Mr Crisp English, Mr Moynihan and Mr Mausell Moullin.

The solitary ulcer of the duodenum has many points of resemblance to the "peptic ulcer of the Stomach" and according to Fenwick (Ulcer of Stomach and Duodenum, P.80) ulcers of stomach and duodenum are associated in 1.7% of all the cases of ulcer of stomach.

In Perry & Shaw's monograph in Guy's Hospital Reports 1894, p.200, of 120 cases of duodenal ulceration 15 had a similar ulcer in the stomach.

Johann Bauhin in 1560 gets the credit of describing the first case, which occurred in a girl who had a history of vomiting blood, but it was not until 1829 that Cruveillier made the subject of "peptic ulcer of the stomach" a clinical entity. The earliest paper on Ulcer of the Duodenum according to Hemmetra is "Das perforierende Geschwür im Duodenum" published in Berlin in 1865 and written by J.Krauss. Since 1865 there has been a very great deal of work done with reference to gastric ulcer, and it has been the rule to class duodenal ulceration as exactly the same, both as regards its etiology and pathology, but there are several differences between the/

the two morbid states and in regard to symptomatology the greatest difference exists. In this thesis I shall endeavour to give a full digest and critical exposition of the etiology and pathology of duodenal peptic ulceration and refer especially to the difficulties in diagnosing the condition before the patient has to pass into the hands of the surgeon, either with a septic peritonitis or else some vague abdominal disorder.

The difficulties of diagnosing a duodenal ulcer are very great when the disease is in its first stage in fact in many cases it is impossible, there being no symptoms whatsoever. Weir (R.F.) in the New York Medical Record, Vol.27, No.18, May 5th 1900, page 749, claims to have made a correct preoperative diagnosis in 13 cases out of 51, but in all these the patients were extremely ill and acute peritonitis, appendicitis, strangulated hernia, hydro-nephrosis, intestinal obstruction, were all diagnosed in cases ^{which} proved to be ulcer of the duodenum.

In order to throw as much light upon the subject as possible, I intend to take up the anatomy of the duodenum in detail first, then the embryology, as far as it bears upon the subject, also the normal histology of the duodenum, so that the morbid changes as/

as shown by my slides may be fully appreciated. The physiology of the duodenal secretions seems to me not to be very well known; but soon, by the aid of Hemmeter's method of intra-duodenal intubation, much more may be worked out; and Hemmeter himself states in his book on "Diseases of the Intestine" Vol.I., page 261, that "Our knowledge of duodenal digestion is still problematic in many respects."

The following are the articles that I have read fully and in the following pages will quote from:

1. Ulcer of Stomach and Duodenum, by W. S. & S. Fenwick, 1900.
2. Guy's Hospital Reports, 1894, Perry and Shaw on Diseases of Duodenum.
3. Diseases of the Intestines, Vol.I. & II. by Hemmeter, 1903.
4. Wilk's & Moxon's Pathology, 1875.
5. Ewald on Diseases of the Stomach, Vol.I. & II. New Sydenham Society.
6. The work of the Digestive Glands, by J.P. Pawlow, 1902.
7. Diseases of the Stomach by Hemmeter.
8. Journal of Experimental Medicine, Vol.II. p.501 by Chas. P. Bardine.
9. New York Medical Record, May 5, 1900. Article by R. F. Weir.
10. Deaver's Anatomy.
11. Lancet, 1890-1904.
12. Hektoens' Pathology.
- 13./

13. Pathology of Skin diseases, by McLeod, 1902.
14. Scottish Medical & Surgical Journal, July 1897,
Article by Cullen.
15. Nothnagels Encyclopoedia, Diseases of the Stomach.

ANATOMY:

The duodenum is the first, shortest and widest portion of the small intestine, being 11 to 12 inches (25-33 centimetres) in length. It does not vary much in size or position and the duodenum has roughly the shape of a horseshoe, the convexity being to the right. Sometimes, however, it is V-shaped. It commences at the pyloric orifice and ends to the left of the body of 2nd lumbar vertebra.

This portion of the small intestine is not very liable to change in position, because it is so firmly anchored to the posterior abdominal wall by the peritoneum. In very marked cases of enteroptosis however, its position is sometimes at a lower level. An extremely rare condition, however, is described by Sir James Paget in Lancet 1841-2, Vol.II., page 58, where the duodenum is described as occupying a hernial sac, and traction of the intestine causing a perforation of a duodenal ulcer in it.

The duodenum also is in close relation to very important/

important structures, viz., it encircles the head of the pancreas, and has the common bile duct and pancreatic duct opening into it.

The duodenum is divided anatomically into three portions. Deaver in his recent text-book on anatomy, describes four portions

1. Ascending,
2. Descending
3. Horizontal
4. Ascending or terminal portion.

1. Ascending or 1st part of the Duodenum usually 5 centimetres long, running transversely from left to right, from pylorus to right side of first lumbar vertebra. It is completely covered by peritoneum, having a mesentery and is freely movable, thus resembling the stomach. At its termination it is in close relation to the neck of the gall bladder, and post mortem is usually stained brown by the bile. Its relations are important, because it is the usual site of the pathological lesion upon which this thesis is written, and the adjacent structures are apt to be affected by the progress of a duodenal ulcer.

Above is the foramen of Winslow with the lesser omentum; below is the head of the pancreas; in front hangs the right lobe of the liver with the neck/

neck of the gall bladder, these being separated from the duodenum by two layers of peritoneum and the capillary space between them. This explains why the liver and gall bladder are not more frequently opened into by perforating ulcers of the anterior wall of the duodenum, because if the condition be at all acute and there be no plastic lymph to obliterate this capillary space between the layers of peritoneum, when the ulcer perforates the wall of the gut a general peritonitis with its very high mortality is the result.

Behind the first portion of the duodenum are:

1. Common bile duct, with the hepatic artery and portal vein coming into relation with it, before the three structures enter the edge of the gastro-hepatic omentum.

2. Gastro duodenal artery with attendant nerve plexuses and lymphatics, this being the artery that most frequently gives rise to fatal duodenal haemorrhage in cases of ulcer. The mucus membrane in the interior of this first portion is not thrown into folds, "the valvulae conniventes" but has quite a smooth surface (see photograph) being similar to the atrium of the stomach.

The/

2nd Portion of Duodenum with Valvulae Conniventes.



↑ 1st Portion of Duodenum. Pyloric fold. ↑ Attrum of Stomach with Smooth mucous membrane. Rugae of Stomach.

The descending portion of the duodenum is about 7 centimetres in length. It extends from the neck of the gall bladder to the level of the third lumbar vertebra on its right side. It is covered anteriorly by peritoneum, the ascending layer of the transverse meso-colon. On its inner and anterior surfaces, except where the transverse colon crosses it, it is in intimate relation to the head of the pancreas, being bound to it by peritoneum and connective tissue. Its relations are, In front, the transverse colon; Behind, the common bile duct, inferior vena cava, right renal vessels, and inner border of right kidney; Internally, Superior/

erior and Inferior pancreatico-duodenal arteries and head of the pancreas.

The duct of the pancreas joins the common bile duct ^{at} as the posterior aspect of this second portion of the duodenum, where having resisted they pierce the coats of the gut obliquely and open into the lumen of the gut at a papilla "The papille of Vater" (vide photo).

The mucous membrane of the second portion of the duodenum shows the transition between the smooth gastric lining and the rugose appearance of the intestinal mucous membrane. The first of the valvulae conniventes usually begins just above the papilla of Vater, in several well marked and long folds, which have the effect of increasing the absorbing surface of the gut to an enormous extent.

The horizontal or third part of the duodenum is the narrowest and longest division, being about 12 centimetres in length. It approaches the calibre and appearance of the jejunum. It runs obliquely upward and to the left across the front of the vertebrae from the right side of the third lumbar to the left side of the second lumbar vertebra. The anterior surface is covered by peritoneum, being bound down to the posterior abdominal wall by the descending/

descending layer of the transverse meso-colon, save where the superior mesenteric artery and vein cross it. Behind this third portion are the crura of the diaphragm, inferior vena cava and the aorta^c. Above it are the pancreas, superior mesenteric vein and artery, and the inferior pancreatic duodenal artery. Below it are the root of the mesentery and the parietal peritoneum of the posterior abdominal wall.

The fourth or terminal portion of the duodenum is the shortest segment, commencing to the left of the second lumbar vertebra, it turns upwards and forward to where the mesentery begins, where it becomes jejunum. Peritoneum covers it on its anterior and lateral aspects; but it is firmly fixed to the posterior abdominal wall, being in close relationship to the left crura of the diaphragm and the tissues around the coeliac axis. There is a band of fibrous tissue containing some muscle fibres, "The musculus suspensorius duodenii" which slings this portion of the gut, holding in position that segment of the intestine known as the Duodeno-Jejunal flexure.

The second, third and fourth portions of the Duodenum are only occasionally the seat of a peptic ulcer/

ulcer, therefore their characteristics are not so important for this paper as the first portion.

Blood Supply of the Duodenum:

The main supply comes from the branches of the hepatic and superior mesenteric arteries. The hepatic artery gives off a branch, the "Gastro-duodenal artery", which runs to the region of the pylorus, where it divides into the right gastro-epiploic artery and the superior pancreatico-duodenal artery, which is the one that most frequently is found opened in fatal haemorrhage from an ulcer. This vessel is situated along the inner and posterior wall of the first portion of the duodenum, and running downwards it joins the inferior pancreatic-duodenal branch of the superior mesenteric artery. These two are the main arterial supply of the duodenum; but in haemorrhage from a case of ulcer other vessels may be opened into, which have a relation to but do not supply the duodenum. These I shall refer to when treating of haemorrhage in cases of ulcer. The veins are numerous and go to join the superior mesenteric vein of the portal system.

The arteries of the duodenum having subdivided till they are of small calibre pierce the muscular coat to reach the submucous coat, where they freely anastomose/

anastomose, so that sudden spasm of the muscle of the intestine will not interfere with the general blood supply. The mucous membrane is richly supplied with capillaries which form a network around the ducts of the glands of Lieberkuhn and send a capillary up each villus in its centre. The venous blood is carried away by an elaborate plexus of venules, which unite to form larger veins in the submucous coat and piercing the muscular coat get outside the gut to form radicles of the portal system.

Nerve Supply of the Duodenum:

The duodenum is supplied probably from two sources - (1) Vagi, (2) Splanchnics. In the gut itself there are two sets of nerve fibrils which form

1. The nerve plexus of Auerbach, which is situated in the muscular coat, and is probably purely motor in its function.
2. The plexus of Meissner, which is situated in the submucous coat and probably contains motor fibres for the muscularis mucosae, vasomotor fibres for the blood vessels, secretory fibres for the glands, and very probably the trophic fibres, which have the peculiar property of keeping up the normal vitality of the cell protoplasm, so that it might resist injurious influences.

That the sympathetic system supplies the uppermost part of the small intestine is undoubted; from the 5th thoracic nerve downwards to the 9th thoracic nerve fibres come off, which run in the sympathetic system, via the solar plexus to supply the small intestine.

The/

The vagus also probably supplies at least the first portion of the duodenum, continuing downward from the stomach, but this point I cannot find proved in any book. The vagus as proved by Pawlow, page 53, does contain vaso-motor fibres with excretory fibres, which are divided into true excretory and trophic fibres for the stomach as far as the pylorus.

The histology of the duodenum is characteristic, especially in its first portion. The peritoneum most external, then the muscle arranged in two layers the outer being longitudinal and the inner circular. They are of non-striped muscle fibres. Internal to them the submucous coat, a layer of loose connective tissue, which contains many blood vessels, nerves and lymphatics, also the glands of Brunner, which are compound tubular glands composed of cells very similar to those found in the pyloric glands of the stomach, granular in character with a deep seated nucleus (well seen in my sections stained with haematoxylin). The ducts of these glands pierce the muscularis mucosae and open between the villi into the lumen of the gut. The ducts are lined with cubical cells, which are also well seen in one of my sections. The secretion of these glands/

glands is very hard to get pure, but when the glands are picked out by means of a dissecting microscope and an emulsion made of them, it is found that their juice contains a feeble peptonising ferment, active in an acid medium, and a sugar inverting ferment.

I shall refer to the role that these glands are supposed to play at times in the production of duodenal ulceration. The muscularis mucosae is roughly composed of two layers and sends slips up toward the lumen of the gut, and also along the villi, its function probably is to assist the flow of fluids both in the vessels and lymph spaces of the mucous membrane.

Internal to the muscularis mucosae are the crypts of Lieberkuhn which are the glands secreting the succus entericus, which according to Pawlow (page 159) augments the activity of the pancreatic ferments, especially the proteolytic. They are simple tubular glands, lined by columnar epithelium. The villi are finger like projections into the lumen of the gut, composed of loose areolar tissue, carrying a capillary loop, with lymphatics and probably nerves. They are covered by a columnar epithelium, the function of which is probably absorptive.

The other important structures which occur in the duodenum are the solitary glands. These are ordinary/

ordinary lymph follicles, either situated in the mucous membrane itself, or in the submucous coat. They may have some bearing at times on the production of an ulcer. The whole wall of the duodenum is thinner than that of the stomach, and this may account for the greater frequency of perforation in duodenal ulcer.

EMBRYOLOGY :

The embryology of the duodenum does not, I think, throw very much light upon duodenal ulceration. The stomach, duodenum and small intestines being originally a straight tube, then a dilatation occurs, forming the primitive stomach, which later comes to lie horizontally and the peculiar curve of the duodenum is due to this change in position of the stomach. I will refer here to a very interesting condition found usually about the end of the first portion of the duodenum, which I think points to a very close relation in development between the stomach and the first portion of the gut. I refer to congenital septae. I do not refer to cicatricial contractions. Perry and Shaw have collected such cases, where the septum was incomplete and resembled an enlarged valvula conniventes. If the septum were complete the child would be certain to die very soon, and such cases seldom come to the post mortem room/

room. Hemmeter, however, quotes a case described by Allen where the first portion of the duodenum ended in a cul de sac, the small intestine commencing quite separately and being about the diameter of a lead pencil. This condition might be analogous to that which occurs at the upper end of the oesophagus in most vertebrates, where at a certain period of development the lumen of the oesophagus is completely obliterated by a septum of cells, thus marking it off from the pharynx (Quain's Embryology, p.104.) It is possible that such a condition might occur in the duodenum, showing that the oesophagus, stomach and first portion of the duodenum were developed from one segment. Also this might be urged to support the idea that the vagus extended into the duodenum, which is embryologically, at least in its first part, the same as the stomach.

Etiology of Duodenal Ulceration.

Sex:

Although very closely resembling the peptic ulcer of the stomach, ulcer of the duodenum is more frequently found in men, the difference between the two sexes being most marked. Fenwick (Ulcer of Stomach and Duodenum) states that duodenal ulcers of all kinds occur four times as often in males; that the so-called chronic peptic variety occurs ten times as often. However, that form of acute ulcer/

ulcer which follows burns occurs ten times more frequently in women. This, however, is probably explained by the fact that women are much more likely to suffer from severe burns of the body on account of their loose clothing and household duties with regard to fires and lamps. Also the ulcer that occurs after burns is not exactly the same as the "Chronic peptic ulcer of the Duodenum".

In the Scottish Medical & Surgical Journal, July 1897, Cullen states that 79% of duodenal ulcers occur in men. R. F. Weir has collected 176 cases, of which 144 were males and 30 females. In Perry & Shaw's cases 52 were in men and 17 in women. My cases only number four, of which three occurred in men and one in^a woman. On adding all these numbers it gives the average of four men to one woman.

Sex has undoubtedly some predisposing relation to peptic ulcer of the duodenum, but how is not quite clear. Boas, quoted by Hemmeter, advances the theory that the habits of man in such matters as smoking and drinking alcohol, predispose him to gastric hyperchlorhydria, which seems to favour the development of peptic ulcer; but if this were the case, it would be expected that man would suffer more frequently from gastric ulcer, which has I think a much/

much more definite relation to hyperchlorhydria. That the greater liberties men take with their stomachs has some bearing upon this question of sex seems to be supported by the experiments of Von Mering (Quoted by Hemmeter). 300 cc. of a 25% alcohol was put into a fasting dog's stomach, in ten minutes 150 cc. containing 10.5% alcohol had passed into the duodenum. Also 200 cc. of 50% glucose was put into an empty stomach and in ten minutes 120 cc. containing 32% glucose had entered the duodenum. This proves that if a concentrated solution be put into a healthy stomach, some of it is passed rapidly into the duodenum in a concentrated state and so relieving the stomach but irritating the duodenum. In man the more fluid contents of the stomach pass into the duodenum first, and the semi-solid food passes along later, so probably very concentrated solutions of fluid constantly are being thrown into the duodenum and irritating it.

However, it seems to me that if this theory held good, then duodenal ulceration should be much commoner than it is. Also the stomach has a sphincter at the pylorus and if it did not let the concentrated and irritating fluid escape soon, the stomach itself would be irritated. However, the duodenum has no such obstruction to the onward flow of its contents, therefore/

therefore if an irritating fluid got into the duodenum it would set up a peristalsis and be moved on.

It seems to me that there are several varieties of ulcer of the stomach and duodenum, and that their ultimate appearance is the same on account of the action of the digestive ferments, as I shall explain later, and that the type which occurs most frequently in the duodenum has as its cause some neurotrophic lesion, and as is well known these vague nerve lesions, especially the trophic lesions, are more frequent in men than in women, viz., Locomotor ataxy is at least ten times more frequent in men. Poliomyelitis Anterior Acuta, Fredreich's Ataxy (86 to 57) Syringo-myelia (133-57), Progressive muscular atrophy, Haematomyelia, Ataxic paraplegia, Poliomyelitis Anterior chronica, Paralysis agitans are all more common in men than in women (Allbutt's System of Medicine).

These facts would explain the greater frequency of duodenal ulcer, if its presence were due to a neurotrophic agency, for all the foregoing diseases have as one of their symptoms some perversion of the trophic influence to the various parts affected. Syphilis and alcoholism are both quoted by some authors as predisposing causes and they both are more frequent in middle aged men, but their influence/

ence on duodenal ulcer is open to doubt. At all events it is not enough to explain the marked preponderance of male over female cases, especially as the lesion occurs frequently in quite young people where alcoholism would probably not have any causal relation.

Frequency of Duodenal Ulceration:

Up to the date of Perry & Shaw's paper in Guy's Hospital reports, 1894, duodenal ulcer seems to have been a comparatively rare disease, but as I pointed out at the beginning of this paper at the present day it is not at all infrequently met with, especially at laparotomies, which I think is "a priori" evidence that the condition often heals in time, because Perry & Shaw's paper was entirely made from post mortem reports.

Perry & Shaw in 13055 autopsies found an open ulcer in 34 cases or 0.26%. Haemmeter quotes 45,869 post mortems, in which ulcer of the duodenum caused death in 108 cases, which gives 0.2355% cases. These figures show that the lesion is not a common one on the post mortem table. Fenwick states also that the lesion is a rare one and compared with gastric ulcer is ten times less frequent. Also it is interesting to note that in his cases of ulcer of the/

the stomach there was an ulcer of the duodenum as well in 17% of the cases. The same author states that open ulcer of the stomach occurs in 4.2% of all post mortems. So he found ulcer of the duodenum in about 0.4% of his cases which is rather higher than other authorities. Perry & Shaw found ulcer of the stomach in 15 cases out of 120 specimens of duodenal ulcer. Taking all the above figures it shows that duodenal ulcer occurs in about 0.25% of all post mortems and that it is associated with ulcer of the stomach in about 1.5% of the cases. Of course these are all fatal cases, during life it is not possible to estimate how frequently duodenal ulcer occurs because so often its symptoms are either latent or extremely vague, but I think that it is not such a very uncommon disease, as is shown by collecting records of gastro-enterostomy for vague gastric trouble. In Lancet of 1903 p.1429 B.G.A. Mognihan quotes 15 consecutive gastro-enterostomies, with two of them cases of duodenal ulcer, occurring in seven weeks hospital work.

Other forms of ulcer occur in the duodenum besides the typical "peptic ulcer" and can easily be distinguished as a rule. Perry & Shaw found in 17,652 post mortems, 25 cases of tubercular ulceration/

tion, three cases of typhoid ulcer, three cases of anthrax causing ulcer, and one case that was typically syphilitic, probably due to breaking down gumma. That such cases should occur shows that all ulceration in the duodenum is not changed into the typical peptic type by the digestive ferments, as has been suggested, but that the peptic ulcer is a clinical entity, and quite distinct from tubercle or syphilis of the intestine.

Age:

The age at which duodenal ulcer occurs is a point of great importance, bearing upon the pathology of the disease. It is essentially a disease of early adult life, but in the following table which I quote from Hemmeter it is seen that children and also very old people are apt to be affected.

Under 10 years of age 42 cases have been collected.

Between 10 and 20 years	24	"	"	"	"
" 20 and 30	" 43	"	"	"	"
" 30 and 40	" 52	"	"	"	"
" 40 and 50	" 46	"	"	"	"
" 50 and 60	" 41	"	"	"	"
" 60 and 80	" 28	"	"	"	"
" 81 and 95	" 30	"	"	"	"

This/

This table shews that more than half of the cases occurred between 20 and 50 years (141 & 125) and that 42 cases occurred under 10 years. These points show that the lesion cannot be due to vascular degeneration. Also when compared with gastric ulcer, it is found that ulcer of the stomach is exceedingly rare before 15 years. Perry and Shaw give the average age of all their cases as 31.3 years, and where the ulcer was the cause of death the age was 43 years. The Fenwicks give the average age of all their cases as 38 years. In their "Acute Ulcer of the Duodenum" 68% occurred between 15 and 30 years, and the chronic variety occurred in 63% of their cases between 30 and 50 years. Therefore according to Fenwick the cases which occur in early life are usually of the acute variety, which he describes as differing in some points from the chronic variety. The ages of my four cases were 22, 23, 28 and 39 years.

The foregoing figures show, I think, that the lesion is one that occurs most often in the prime of life, before the onset of degenerative changes. It is the age, however, at which both alcohol and syphilis are most frequently met with, and Boas, Burwinkle and Boucquoy are quoted by Hemmeter as giving alcoholism as a predisposing cause to ulcer of/

of the Duodenum. The fact that the lesion occurs in children so frequently shows that the influence that alcohol may have cannot be very great. Also, alcoholism is of very frequent occurrence in hospital patients and it would be expected to find ulcer of the duodenum more frequently than in 0.25% of all post mortems, if the influence were marked.

With regard to syphilis, it may have some predisposing influence, for children often suffer from the hereditary form of the disease. Also *Meloena neanatorum* which may be syphilitic in origin, often is associated with haemorrhages or even ulcer in the duodenum, according to Merkel, Nothnagel and Pavensky, quoted by Hemmeter. Fenwick found syphilis associated with ulcer of the duodenum in 6% of his cases, but any direct relationship between the two diseases has yet to be made out. It might be that syphilis gave rise to a peculiar friability of the vessels in the duodenum, so that submucous haemorrhages would more easily occur, or even an endarteritis and so support the vascular theory as to the starting point of the ulcer, but it is also possible that syphilis might act through the nervous system, that it does so at times is seen well in locomotor ataxy, which is almost always post syphilitic.

Associated/

Associated Diseases:

I have mentioned syphilis as an associated disease in 6% of the cases, according to Fenwick.

Alcoholism does not seem to me to have any very direct bearing upon the lesion, as I have already pointed out.

Tubercle by some is supposed to be often associated with duodenal ulcer, and it is frequently met with in cases of gastric ulcer. It seems to me that when recent tubercular lesions are found in a person who has died from ulcer of the duodenum it is quite possible that the ulcer has so lowered the vitality of the individual that the ubiquitous tubercle bacillus has found a suitable soil. That the actual ulcer is not tubercular is supported by the fact that typical tubercular ulcers occur both in the stomach and duodenum and are very different from the typical peptic ulcer, both to the naked eye and under the microscope. Perry & Shaw quote 25 cases where tubercle was associated with duodenal ulceration. In 11 cases the ulcer itself was distinctly tuberculous, the ulcers being small and usually multiple, as if the solitary glands were affected. In several cases typical miliary tubercles were seen in the serous coat. Their youngest case was aged 11 and the oldest was 36; 6 were males. Also they found/

found 14 cases of typical peptic ulcer with tubercular lesions elsewhere in the body. Fenwick states that tubercle is associated in 17% of his cases, but tubercle is very frequently met with at post mortems, and I should think that at the present time traces of tubercular disease could be demonstrated either microscopically or bacteriologically in fully 17% of all post mortems. In neither of my sections was any trace of tubercular disease found in the abdominal viscera.

Nephritis in its various types has been met with in cases of duodenal ulceration, and I think that the association must have been more than accidental. Perry & Shaw quote 16 out of ^{cases} 70 where Bright's Disease was associated with ulcer of the Duodenum.

With reference to the association between Gastric hyperchlorhydria and duodenal ulceration there is not much literature available. Richmann in 1882 first drew attention to the close relationship that an excessive secretion of HCl had to gastric ulceration. Fenwick states that the two conditions were present in 72% of his cases, and quotes Rosenheim who found it present in 66% of his cases. In ulcer of the stomach this excessive secretion may quite well be due to the presence of the ulcer acting reflexly. Pawlow (p.171) had the opportunity of observing/

serving the development of a round ulcer in a miniature stomach of a dog and found that during the development of the ulcer the HCl secretion increased till it exceeded the normal 3 or 4 times, and he argues from the pathological curve of the secretion per hour that the glands, the centrifugal nerves, and the corresponding nerve centres were normal, and that the increased secretion was reflex and due to lesion either in the centripetal nerves or their nerve endings. Rokitansky and Camerer quoted by Ewald stated that hypersecretion is due to paralysis of fibres in the vagi, and I think that when these points in the pathology of peptic ulcer are investigated, this theory of a reflex hypersecretion will be found correct.

With reference to the duodenal ulcer Hemmeter in three cases found hyperchlorhydria in one case and the HCl normal in two cases. He also quotes Boas, Devie Rou and Robin, who found hypersecretion to be the rule, whilst Leube and Richmann found subacidity to be the rule. From these facts it seems to me that an excessive secretion of HCl has no causal relationship to duodenal ulcer, but when it occurs it is either due to the same cause as the ulcer, a degeneration of certain fibres in the nerves supplying the viscus, or else it is due to the presence of the ulcer acting reflexly upon the HCl secreting mechanism.

Morbus Cordis According to Perry & Shaw heart affections do not have any causal relationship to the peptic ulcer of the duodenum. Fenwick, however describes a type of duodenal ulcer that sometimes occurs in the course of Ulcerative endocarditis and pyaemia but this ulcer is essentially the same as that which occurs in any septic condition, especially when of the skin as in burns.

Anaemia occurs in 72% of acute gastric ulcers, but it does not seem to have any relation to duodenal ulcer. A secondary anaemia occurs after a severe haemorrhage from a duodenal ulcer, and such a morbid condition of the blood may retard the healing of the ulcer. This is proved by Silbermann, who found that artificial ulcers did not heal rapidly if the animals had been rendered anaemic. (Nothnagel's Encyclopaedia, p.568.)

Site of the Ulcer:

The type of ulcer known as the "Chronic peptic ulcer" is found almost invariably in the first portion of the duodenum; it is extremely rare to meet with it below the level of the bile papilla. Most frequently it is to be found immediately beyond the pyloric ring. The "raison d'etre" for this seat of election/

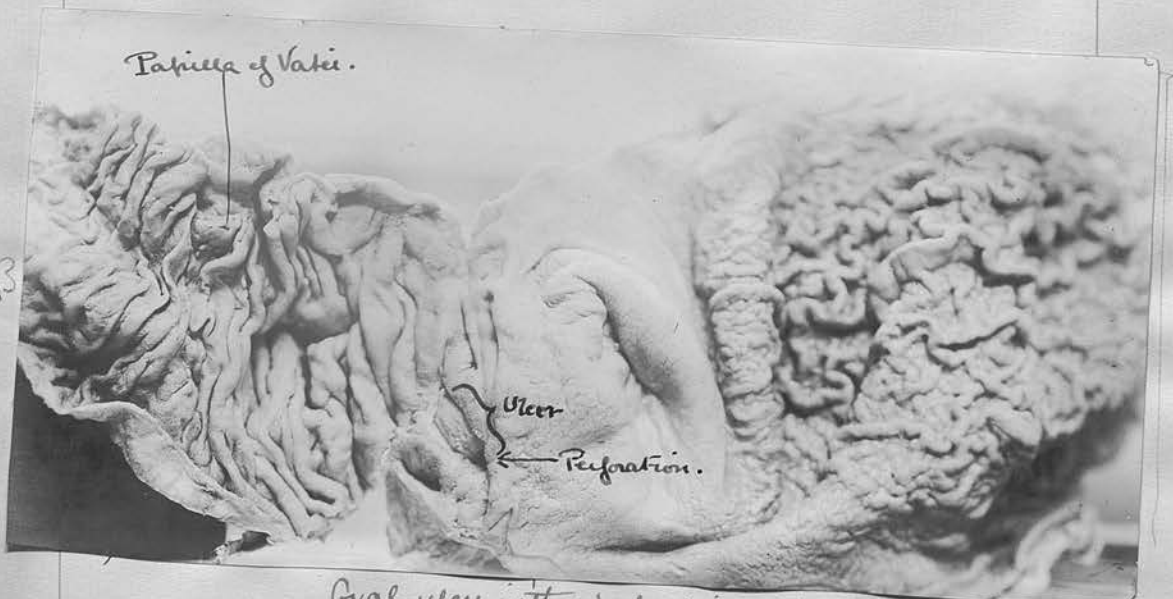
election for duodenal ulceration is obscure. In the discussion upon pathogenesis I shall endeavour to point out how some of the theories of causation act upon the whole of the duodenum, for instance it is impossible to imagine that emboli that reach the duodenum should always lodge in the first portion, which has no highly specialised mode of blood supply. In the records at my command I find that in 149 cases Perry & Shaw found the ulcer in the first portion no less than 123 times, 16 times in the second portion, 2 times in the third portion, and in 8 cases the ulcers were multiple. I shall point out that multiple ulcers have probably a different pathogenesis to the typical single ulcer.

Fenwick states that 82% of his cases occurred in the first portion of the gut; also the same author found that 86% of his duodenal ulcers were solitary. Collin, quoted by Hemmeter, gives 262 cases of perforation of duodenal ulcers, and in 242 cases the perforation was within two inches of the pylorus. These figures show how large a proportion of the cases occur near the pylorus and I would suggest this is explained by looking upon most of these chronic ulcers as the result of a nerve lesion, the nerve affected being the vagus probably, and its peripheral fibres, especially where they enter the/

the first portion of the duodenum to join the plexuses of Auerbach and Meissner. However, I will discuss this theory at length further on. It is of interest to find that Fenwick describes a "chronic ulcer of the stomach" that occurs up to middle age where 76% of the ulcers were situated in the region of the pylorus, and that such ulcers are single in 87% of the cases. As can be seen in my photos in both my cases the ulcer was very close to the pylorus.



↑
Pyloric Papilla. Round ulcer with serrated edges, & perforation in the floor.



Papilla of Vater.

Ulcer
Perforation.

Oval ulcer with a perforation at its lower end.

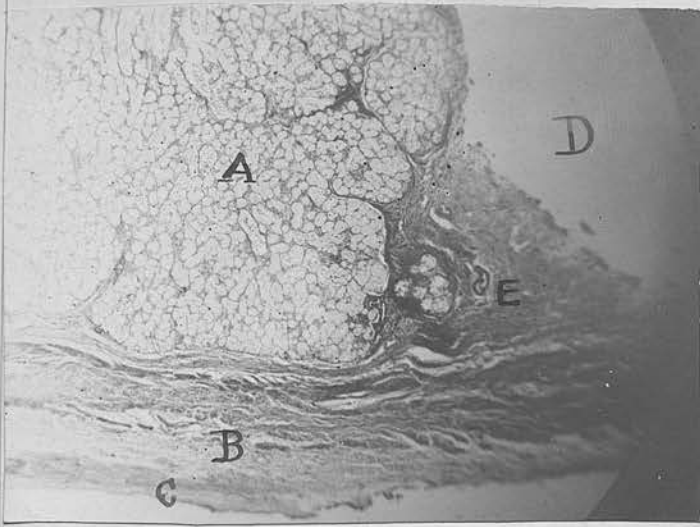
Number of ulcers present:

The great majority of the type known as "Chronic peptic ulcer" are single. Perry & Shaw in 160 cases found the solitary ulcer in 137. Fenwick states that 86% are single. Morin quoted by Fenwick, found that 81% were single. This is of interest because the type of ulcer that is found after septic conditions is usually multiple, showing that probably the pathogenesis of the two conditions is not the same. Multiple ulcers are not as a rule confined to the first portion of the duodenum, but may be found even in the third portion. Multiple ulcers are found to be of the acute variety as a rule.

Pathological Anatomy.

I have already described how the "Chronic peptic ulcer" of the duodenum is usually single, and occurs close to the pylorus. In shape it is usually circular, but it may be quadrilateral. My photos show an example of either type. The ulcer may occur on any aspect of the gut, but usually is found on the posterior and lower wall of the first or horizontal portion (according to Berry & Shaw). Both of my cases were on the anterior wall, and as can/

can be imagined such ulcers most readily give rise to perforative peritonitis, which was the cause of death in both my cases. The ulcer that is situated on the posterior wall, lies over the region of the larger blood vessels and therefore gives rise to haemorrhage more frequently than the ulcer on the anterior wall. In my two post mortem cases there was no history of haemorrhage, nor any haemorrhage whilst they were under observation; in my two cases which recovered the haemorrhage was the outstanding feature, therefore I argue that in them the ulcer was on the posterior wall and that such cases are less liable to be fatal than the type where the ulcer is anterior. Fenwick states that 35% of cases of ulcer of the duodenum die from haemorrhage, I think that haemorrhage must occur in every case of duodenal ulcer, but that it is usually small in quantity and passed partially digested in the faeces. Such haemorrhage would easily be overlooked, especially as patients with an ulcer of the duodenum usually have no marked symptoms. The ulcerative process probably being a digesting away of a portion of the mucous membrane that is below par will open any small vessel that it comes across, and in my sections vessels may be seen extremely close to the surface of the ulcer which are not thrombosed and which would certainly bleed if opened. As the ulceration/



Microphotograph
of
Edge of ulcer
as seen in
Slide I A

- A. Glands of Brunner.
- B. Muscular coat.
- C. Peritoneum
- D. Free surface of the ulcer
- E. Small blood vessel, that is not thrombosed and in the living body would probably bleed if it were opened.

ulceration extends deeper into the submucous or muscular coat larger vessels may be opened, and when the ulcer is on the posterior wall the main vessels may be opened. When on the anterior surface the ulcer opens into the peritoneum without encountering any very large vessels, which explains the fact that many cases of perforation have no history of haemorrhage. On the posterior wall the ulcer may even invade the pancreas and the bleeding may come from the vessels of that organ, as described by Perry & Shaw in 18 cases. The vessels from which fatal/

fatal haemorrhage usually comes are, Superior Pancreatico-duodenal artery; Collin gives 12 cases, Fenwick 10 cases, Perry & Shaw 9 cases. Fenwick also found records of the following vessels being opened into -- Gastro-duodenal artery, 3 times, and once in each of the following vessels, Pancreatica magna, branch of the Splenic, Hepatic, Inferior Vena Cava, Portal Vein, and abdominal aorta. This shows that when there is much haemorrhage the ulcer is probably posterior.

The circular shape of the ulcer is not so well marked in the duodenum as in the similar ulcer in the stomach, and the cause of this circular shape has been the subject of a great many theories. Virchow explained the circular shape by assuming that the ulcer was caused by an embolus and that an infarct of the duodenal mucous membrane was caused, which, from the nature of the distribution of the ultimate branches of the thrombosed vessel, was circular in outline. This would explain the shape of the ulcer if an embolus was the cause, and I shall discuss the embolic theory further on in this paper. In my opinion the correct explanation of the circular shape of the ulcer is as follows: The lesion must start at some given point, and it is admitted by most authorities that the progress of the ulcer is/

is caused by the digestive action of the HCl and pepsin of the gastric juice. In the first place such extension would naturally spread from the centre and make the enlarging ulcer more or less circular as long as it was superficial. In the second place, when the ulcer has extended down as far as the muscular coats, this coat is at first irritated by the HCl., and the fibres thrown into contraction and remain irritated till they die. The muscular tunics (muscularis mucosae and muscle wall proper) being composed of fibres that run in all directions, the action of these fibres around the damaged area will tend to make that spot circular by the equilibration of tension. This equilibration of tension theory would also explain the terracing of the sides of the ulcer, and also in the duodenum where the ulcer is quadrilateral, this could be explained by the fact that a certain layer of the muscle had been reached and its action had preponderated. For instance, if the inner layer of the muscular tunic had been markedly irritated, and a break in the muscle had been caused by the digestive agents, then this muscle would by its contraction tend to cause the ulcer to be oval in the transverse axis of the gut. Sometimes it is found that the mucous membrane is undermined (Fenwick) which supports the theory of "contraction of muscle/

of muscle fibres, as a cause of the circular outline of duodenal ulcers". It is also to be borne in mind that the muscular tunic of the stomach is in three layers (cf. muscle fibres running in different directions) therefore the ulcers are more often circular than where there are only two layers of muscle fibres running at right angles to one another. In acute cases, the outline is often irregular, but their pathogenesis I consider to be entirely different from the "Chronic Peptic Ulcer". In my photos the circular ulcer with the terraced sides is most beautifully seen, especially if looked at with a convex glass. The oval ulcer is also shown with its long axis running round the gut.

The floor of the ulcer is invariably perfectly smooth, unless the floor be formed by an abscess cavity in some neighbouring structure, such as the pancreas. Granulations have been described by Muller in 1872, quoted by Hemmeter, but no other observer has described them, and I think it is extremely doubtful if they occur, in the ordinary sense of the term. These ulcers, if small, have been shown to heal by a proliferation of gland and connective tissue elements in their walls. If they are large they heal by fibrous tissue which being deposited in the base of the ulcer contracts till the sides are in apposition/

apposition, sometimes causing very great distortion of the organ in the process of healing, e.g. Trifid stomachs and stenosed pyloruses. It must be remembered, however, that post mortem appearances are very different to that which is present during life, especially in stomach lesions. Personally, I have seen several cases of perforated gastric ulcer which when handled on the operating table seemed to be surrounded by a thick oedematous ring about one inch in thickness and two inches across, and these cases in the post mortem proving to be punched out, typical gastric ulcers. It remains with the abdominal surgeon to discover if granulation tissue is ever found covering the base of a gastric or duodenal ulcer. Very often plastic peritonitis occurs over the base of the ulcer, leading to adhesions with other abdominal organs. If the floor of the ulcer be adherent to the pancreas, or to the liver, the subjacent organ becomes sclerosed, due to the irritation from the ulcer.

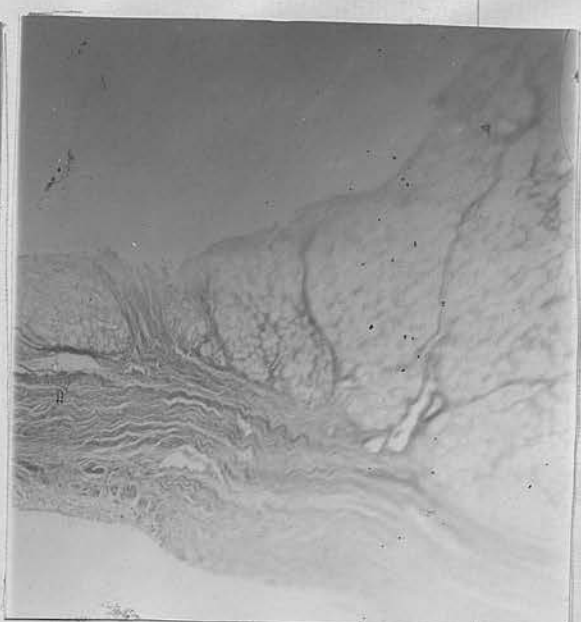
An interesting condition has been described by Perry & Shaw as occurring in connection with duodenal ulcer, and that is the formation of duodenal pouches. I have never seen a well marked case, but in case No. II. of mine the floor of the ulcer was bulging to some extent. Pouches seem to be fairly common in the duodenum as pathological curiosities, a hernia of all/

all the coats of the gut, 10 cases are described by Perry & Shaw, all being between the papilla of Vater and the Pylorus. They do not seem to be associated with duodenal ulcer, although Fenwick states that they may occur in the wall of the gut opposite the ulcer. They occur in about 6% of all cases of duodenal ulcer. Their pathogenesis is obscure, probably the intra intestinal pressure is highest in the duodenum, being so near the stomach which acts as a vis a tergo to the intestinal contents, and the passage onwards of the intestinal contents being delayed by the contents of the jejunum and ilium. They seem to be more frequent in patients who have a history of constipation (Perry & Shaw). They do not seem to be of congenital origin, for only in one case was there found any other congenital abnormality, a Me^Skel's diverticulum, nor are they traction pouches, for there were no adhesions present in the 10 cases described. If this theory of great intra-intestinal pressure be correct, it would help to explain the great frequency of duodenal perforation. The other reasons why duodenal ulcers perforate more often than gastric ulcers ^{be} being the difference in the thickness of the walls of the organs, the duodenal walls being much the thinner. Sometimes the wall of the duodenum is/

is so weakened by the presence of the ulcer that it bulges, the ulcer forming the apex of the pouch. This was seen to some extent in my second case.

Microscopically:

When a section is cut of a duodenal ulcer of the chronic type the most marked phenomenon is, I think, the apparent absence of any inflammatory reaction in the tissues of the gut surrounding the ulcer. In my sections of the ulcer of Case II. although marked fibrous tissue deposit has occurred outside the peritoneum, the tissues of the gut, mucous membrane and submucous coat do not show any fibrous tissue change, and not much small cell infiltration. I shall describe my sections in detail with the records of the cases. Fenwick, Hemmeter, and Perry & Shaw give the following general description of chronic ulcer. There is not much inflammatory reaction as a rule; the adjoining Lieberkuhn glands may be obliterated by fibrous tissue, but are often apparently digested away down to a certain level, without much other change. (This point is well seen in my sections.) The vessels in the immediate neighbourhood of the ulcer often are obliterated by organised thrombi and degenerated nerve fibres are found in the submucous coat. It is/



A/

B/

Microphotographs showing the absence of small cell infiltration in the walls of the ulcer. A/ from slide II.A. B/ from slide I.B.

is impossible to say if the obliteration of the vessels is the cause or the effect of the ulcer and the same may be said about the degenerated nerves that are found, but ^{but in one} my sections of Case II. show in an extremely interesting manner many vessels quite close to the base of the ulcer, apparently fairly normal, and a nerve fibre which undoubtedly shows an interstitial overgrowth of fibrous tissue, thus in one case proving that the vessels were not the cause of the ulcer, but the nerve might be. In section I., although no nerve fibrils could be seen in any of my sections, small vessels quite close to the base of the ulcer are apparently healthy.

The fibres in the muscular coat often show fatty degeneration and if the ulcer has been of long duration/

duration overgrowth of connective tissue may be observed in the muscular and submucous coats. The cells of the adjoining glands of Brunner and Lieberkuhn often stain badly, and may show cloudy swelling.

Fenwick, page 26, states that the fibrous tissue overgrowth in the connective tissue between the ducts of the glands may cause obstruction and retention cysts in the obstructed glands. Owing to the retraction of the muscularis mucosae the ducts of the glands may at times be displaced so that they seem to open into the ulcer. This fact gave rise to the theory propounded by Witosowski, that these glands poured their secretion into the ulcer and so prevented it healing. This theory is probably erroneous because the immediately adjacent glands would have their function seriously interfered with. Openchowski has also noticed hyaline degeneration of the vessel walls in the base of the ulcer, probably merely a degenerative change, secondary to the ulcer and not a causal agent.

The microscopical appearance of an acute ulcer differs markedly from the chronic ulcer in having evidence of haemorrhage and great small cell infiltration in the immediate neighbourhood of the ulcer.

The ulcer that is met with after burns is of the acute type, often multiple, irregular in outline, with at times evidences of haemorrhage at the base of the ulcer, as if the mucous membrane had been digested away over a submucous haemorrhage.

PATHOGENESIS.

In discussing the actual cause of Duodenal ulceration it is necessary to divide ulcers into two great classes: 1. Acute; 2. Chronic.

It is the so-called chronic type of ulcer that I have cases of, and with which this thesis is supposed to deal, but after an acute onset it is quite possible that an ulcer may ^{persist} for some time taking on the character, both macroscopically and microscopically of the typical chronic peptic ulcer.

In studying the pathology of both acute and chronic ulcers it is to be remembered that the further progress of the ulcer, after the initial lesion which has caused a lowering of vitality at a special point, is due to the action of the gastric digestive ferments. Most authorities seem to agree upon this point and the arguments in its favour are as follows:

1. The characteristic ulcer is only found where the HCl and pepsin are normally present, lower end of oesophagus, stomach and first portion of duodenum. I do not see any argument against trypsin acting in a similar way, in lesions of the intestine, but it does not.

2. The character of the ulcer under the microscope; no inflammatory reaction, no evidence of sloughs/

sloughs, the structures of the gut seem to be dissolved away down to a certain level, a necrobiosis of the part affected.

3. The circular outline and terraced sides of the ulcer may be urged as arguments in favour of its progress being due to the action of digestive juices.

4. In carcinoma of the stomach, it is well known that HCl. is almost always extremely deficient and in cases that have come under my own notice the tumour has projected into the lumen of the pylorus and has been ulcerated, but in such a case the ulcer had a shaggy base and ragged edges and quite unlike a peptic ulcer, showing that in the absence of gastric ferments ulcers may occur in the stomach that are similar to ulcers that occur lower down in the digestive tract and have not the characters of a peptic ulcer. In the two cases of carcinoma ventriculi that I quote, there was complete absence of HCl. in the stomach contents.

Although the cause of the spread of a duodenal ulcer is fairly clear, it is necessary before the HCl. and pepsin can act, to have either a breach in the continuity of the mucous membrane, or else a point where the vitality of the mucous membrane is "below par". Why the mucous membrane of the stomach/

ach is not digested by its own secretion is one of the unexplained phenomena of physiology, and one is driven back to the "vitality of the individual cells" to answer the question. Edinger, quoted by Nothnagel, p.561, has proved almost conclusively that the whole thickness of the gastric mucous membrane has an acid reaction, and I think this must be so, for the HCl. secreting cells themselves must be acid, at least the lumen of the acinus in their immediate neighbourhood must be acid. In the duodenum I think that so far as the muscularis mucosae will be acid, and probably the glands of Brunner will be alkaline like the blood. I consider that these facts prove that Pavy's theory that the alkalinity of the gastric mucous membrane protects it from the action of the HCl. under normal conditions must be erroneous. Enriquely in the Lancet of 1904, p.762 describes that in cases of muco-enteritis and intestinal dyspepsia, acid medication of the duodenum has proved favourable, thereby showing that in normal man the duodenal secretion is acid and exerts a stimulating action on the other secretory functions of the glands of the intestinal tract. Acid contents of the duodenum excite a secretion in the pancreas has been proved by Pawlow.

Ewald, p.434, states that normal gastric juice, if the/

if the constitution of the blood be normal neither causes the development of an ulcer, nor favours its progress, nor checks its healing. If this statement be correct, it is clear that there must be some other influence at work besides the initial lesion, especially in certain cases of duodenal ulcer, where before either a large haemorrhage or perforation occurs, there is absolutely no evidence of change in the gastric juice or of the blood.

Acute ulcer of the duodenum is a well marked clinical entity and according to Fenwick may be classified as follows:-

1. Acute primary ulcer, which is extremely rare occurring in men of from 18-30 years of age. The pathology of this condition is very obscure; but to my mind it is probably the same as that of the chronic peptic ulcer which I will discuss later.

2. Acute secondary ulcer, the most typical example of which occurs as a result of extensive skin burns, or sloughing of large areas of skin (Billroth, quoted by Perry & Shaw, p.188). Recently, it has been urged that duodenal ulceration after extensive burns is not so common as used to be taught, (Encyclopoedia Medica, "Duodenal ulcer") but according to Perry & Shaw such ulceration occurs in 3.3% of all burns, whilst it only occurs at most in .25% of all post mortems. Erichsen & Holmes in their System/

System of Surgery have collected 125 cases of burns with 16 cases of ulcer. Curling in a paper in Vol.25, Medico Chirurgical Transactions, p.260, collected 10 cases, with ages ranging from $3\frac{1}{2}$ -28 years and the symptoms of ulceration appearing from 8-37 days after the burn. Four of their cases died of haemorrhage, and three from perforation of the gut. Perry & Shaw, p.192 collected 19 cases with ages ranging from 4-70 years and death occurring from 4-75 days after the injury, and in ten of their cases there was neither haemorrhage or perforation. These facts show that the lesion may occur at any age, and comes on as a rule where there has been time for septic infection to occur in the skin and supports the theory that absorption of toxins from a large superficial area has some bearing upon the duodenal lesion. Billroth states that duodenal ulcer occurs after extensive sloughing of the skin from any cause in the same percentage as after burning, 1 ulcer in 37 cases of skin sloughing and 1 in 30 of burning, (Perry & Shaw, p.190.)

The cause of the duodenal ulcer occurring as a result of a superficial burn is somewhat obscure. Unlike the chronic peptic ulcer they are often multiple, two or three ulcers being present; but they are almost invariably situated above the bile papilla/

illa. Perry & Shaw found in 29 cases, 22 had the lesion in the first portion, four in the second, and three in the third portion of the duodenum, and of these 29 cases 16 had a single ulcer, showing that most ulcers occur where Brunner's glands are most numerous and also where the HCl. and pepsin are present.

Although a great deal of work has been done with reference to etiology of ulcers following burns, the exact relationship between the two is still problematical. Charles R. Bardine, in the Journal of Experimental Medicine, Vol.II., page 501, has written an elaborate article upon the subject, and finds the following morbid changes chiefly in the blood

1. Marked Leucocytosis.
2. Specific gravity increased.
3. Red blood cells injured physiologically and morphologically.

In the cells of the spleen, marrow and lymph glands debris of the red blood cells occurred, and pigment granules were found in the epithelium of the kidneys, also some of the smaller veins of the abdominal viscera were found thrombosed. These facts show, I think, that there is undoubtedly a marked blood change after burning, such as might be caused by toxins circulating in the blood either from sepsis or/

or some special toxin absorbed from the burnt skin. Kijanitzin, quoted by Hemmeter, claims to have isolated a toxin or ptomaine from the blood and organs of animals which had been severely burnt, and that this ptomaine when injected into other animals caused especially diarrhoea and meloena. Fenwick isolated an albumose from burn sloughs which when injected into dogs caused a duodenitis. These facts show that there is some special toxin circulating in the blood after burns, but why this should affect the duodenum especially is hard to prove. Curling, at Bowman's suggestion, associated this type of ulcer with lesions of Brunner's glands, and it is quite possible that if the glands of Brunner were inflamed and swollen, or if they became cystic, the mucous membrane over them would be stretched and have its vitality impaired, and so be either liable to rupture or digestion by the gastric juice. No physiological relationship has yet been established between the skin and Brunner's glands. In view of our most recent knowledge, I think the correct explanation of these duodenal ulcers is as follows. It is well known that the intestinal glands of all kinds secrete foreign substances from the blood into the gut, seen well when morphia is given hypodermically; it can be found/

found in the stomach soon afterwards. According to Binet, quoted by Fenwick, p.111, iodide of potash and most alkaloids were excreted into the stomach; also the gastro-enteritis of nephritis is due to the excretion of urea by the intestinal mucous membrane. The only glands that are peculiar to the duodenum are Brunner's glands, and I think they must have some special affinity for the toxin caused by skin burns, and whilst excreting it they are irritated, inflamed and give rise to the characteristic ulcer. The other theories that have been advanced are all open to criticism. If the condition were due to septic emboli, why should they so often lodge in the first portion of the duodenum? It has been shown that when artificial emboli are thrown into the blood stream, very few reach the duodenum compared with the stomach, yet this type of ulcer seldom occurs in the stomach as compared with the duodenum. If the lesion be due to inflamed solitary glands the same argument holds good, for it would be expected that the lymph follicular tissue of both stomach and intestine would be affected as well. Bardine found marked swelling of all the solitary glands in the bodies of five burnt children that he examined.

It has been suggested that the bile excreted the irritating body, it may do and cause the congestion/

tion of the iléum and jejunum that is so commonly met with after burns; but the ulcer occurs in the first portion of the duodenum above the entrance of the bile. Another theory as to the cause of those acute ulcers is that there is an acute inflammation of all the intestine associated with sub-mucous haemorrhages and probably petechial erosions are subject to the action of HCl. and pepsin and so spread, whilst the intestinal haemorrhages do not. If such were the case, why does the lesion not occur more frequently in the stomach which always is affected in this form of gastro-enteritis? and why so often only in the first portion of the duodenum?

This type of ulcer seems to heal readily, so probably it occurs much more frequently than the post mortem records show; it is seldom diagnosed unless there is either marked haemorrhage or perforation, which are very often fatal. If neither of these accidents occur, then the symptoms are vague pain, and probably vomiting and diarrhoea, which are exactly what we would expect from a gastro-enteritis which is so very common after superficial burns. At times when the patient has died from either haemorrhage or perforation distinct signs of healing/

healing of other parts of the ulcer have been observed. Also scars of old duodenal ulceration are found where the patients have had a history of burns. Haemorrhage is the usual cause of death, perforation being the exception (Fenwick, p.158)

When discussing the chronic type of ulcer it must be remembered that if from any cause these acute ulcers do not heal rapidly they may persist and have all the characteristics of the chronic ulcer.

My personal experience of post mortems on cases of burns is limited to six cases, three of whom died within 48 hours, one after 4 days, one after 9 days, and one 18 days after the injury. In no case was there any duodenal ulcer, but in the latter three cases there were haemorrhages in the intestinal mucous membrane, and in the one that died after 9 days there were superficial erosions in the stomach.

It is interesting to note that Brunner's glands have been found enlarged and evidently inflamed in other conditions as well as in burns, and in all cases the original morbid condition was the result of organismal invasion. According to Perry & Shaw, these glands were affected in two cases of phthisis, two of typhoid, one lobar pneumonia, three cases of gangrene/

gangrene of limbs, four cases of Asiatic cholera, one of endocarditis, and two of pyaemia. Also they were found enlarged in two cases of chronic nephritis and one case of Addison's disease, in which conditions it is well known that ptomaines are present in the circulation.

In these acute ulcers hypersecretion of HCl. does not seem to have any causal relationship. Fenwick states that acute duodenal ulcer may occur after frost bite; this is quite probable, I think, for the sequelae of frost bite are very similar to those of superficial burns if sepsis supervenes.

Theories as to the cause of Chronic
Peptic Ulcer of the Duodenum.

As with chronic gastric ulcer the cause of this interesting condition has evolved many theories. By most authors the two conditions, chronic gastric and chronic duodenal ulcer are looked upon as identical. But the difference of sex and age seem to point that there is some difference between the two morbid conditions.

I think that the condition of chronic peptic ulcer may be the result of several agencies, but the resulting ulcers are similar in their symptoms and/

and appearances. In the duodenum many of the causes of stomach ulceration do not play such an important role and if we can discover the most frequent cause of chronic peptic ulcer of the duodenum, then the same cause will probably hold good in that large number of gastric ulcers, which occur in middle age without the presence of chlorosis, where the etiology and pathology are not at all clear.

I have already stated my views with regard to the action of the HCl and pepsin in stomach and duodenal ulceration. Given a damaged area or spot, the tissues where the vitality is lowered are acted upon by the digestive ferments and the characteristic peptic ulcer results. Fenwick (p.99) describes the following experiment. "If the stomach of a dog be mechanically injured, or if submucous haemorrhages be induced in it by section of the cervical spinal cord, definite ulcers are produced if HCl and pepsin be present in the stomach; if, however, the contents of the stomach be rendered neutral or alkaline then these ulcers are not formed. Ordinary ulcers produced in the stomach experimentally heal with great rapidity, therefore we must look for some agency that prevents this healing in the human stomach and duodenum at certain times. I will now discuss the theories as to the cause of the initial necrotic area in the Duodenum.

1. Virchow's Embolic Theory: Virchow first pointed out the similarity of a perforating ulcer and an infarct of the kidney, and thought that the peptic ulcer was due to an embolus of one of the gastric or duodenal arteries. Many experiments have been made on this subject. Panum used an emulsion of wax, Cohnheim powdered chromate of lead, Fenwick (p.101) used tobacco seeds. All observers found that where an embolus lodged in a gastric vessel extensive ulceration occurred. In the human subject the usual cause of emboli are (1) vegetations or clots from the heart in morbus cordi, but I have pointed out that Perry & Shaw could find no causal relationship between morbus cordis and duodenal ulceration; (2) Clumps of micro-organisms in cases of pyaemia, these may sometimes give rise to acute ulcer of the duodenum, but such ulcers are usually multiple and not confined to the first portion, and I do not think such emboli could be the starting point of a chronic duodenal ulcer without obvious antecedent symptoms. (3) Clumps of disintegrated red blood corpuscles; but such a condition is not found in the human body except under exceptional circumstances, e.g., after burns, malaria, and poisonings with haemolytic agents. The main argument against this embolic theory is cases of duodenal/

duodenal ulcer is, I think, the fact that experimentally so few emboli ever lodge in the duodenum, and if one did reach the duodenum, there is no apparent reason for it always lodging in the first portion. Therefore the embolic theory may occasionally account for an ulcer in the stomach, but much more rarely, if ever, can it cause the duodenal ulcer. Besides the embolus there would need to be the same morbid condition to prevent the ulcer healing, for duodenal arteries are not endarteries and experimental ulcers heal rapidly, as I have pointed out, unless some other morbid condition be produced which interferes with healing, such as secondary anaemia, or artificial hyperchlorhydria.

2. Thrombosis or Endarteritis might so interfere with the nutrition of an area of duodenal mucous membrane that ulceration could be set up. However, such a condition is not common. Ulcer of the Duodenum occurred in my list of 42 cases under 10 years of age, when endarteritis is an excessively rare disease. Also thrombosis in the vessels of a young adult, without any obvious illness is not a common condition, and limited to the duodenum, it must be excessively rare. As a cause of ulcer, I do not think that either thrombosis or endarteritis/

endarteritis plays an important role in the duodenum. But as a cause of preventing the repair of an ulcer they may exert a very considerable influence; but in my two series of sections no organised thrombosis were found in any slide either in arteries or veins.

3. Venous obstruction has been advanced as a cause of ulcer in the stomach by Muller, quoted by Fenwick, and undoubtedly when the portal vein is tied ulcers and submucous haemorrhages do occur in rabbits' stomachs, yet no ulcer occurred. As a cause of duodenal ulcer this vascular condition has little or no influence.

4. Vascular spasm is advanced by Klebs as a cause of ulcer (Handbuch d. path. Anat., Bd.I. p.185, 1869). Talma, quoted by Fenwick states that on Faradising the left vagus tonic spasm of the pylorus results, and as the vessels around the pylorus pass very obliquely through the muscular coats such a spasm would cause considerable vascular disturbance. If the stimulation of the nerve be carried on for six hours and the animal then killed, ulcers are found around the pylorus (Fenwick, p.106). In support of this theory Talma gives the fact that in three of his cases of gastric ulcer intense pain was experienced/

experienced before the onset of haematemesis. This premonitory symptom is very uncommon according to Fenwick. I think spasm of the pylorus might start an ulcer, but only explained by an elaborate hypothesis, Gastric hyperchlorhydria, according to Fenwick (p.300) is invariably associated with pyloric stenosis or hypertrophy when not associated with ulcer. This stenosis may be due to the constant attacks of spasm in the muscle causing it to increase in thickness. In cases of hypersecretion of HCl. pain is a constant phenomenon, Fenwick p.301, and I think it is ^{not} impossible that at some time due to this pyloric spasm a haemorrhage might occur which would be the starting point of an ulcer, because of the excess of HCl. being present. In the duodenum, however, pain is not a common symptom before ulceration occurs.

5. Vascular spasm may be due to a vaso-motor influence apart from spasm of the pylorus, and according to Pawlow, p.53, vaso-motor fibres do run in the vagus to the stomach, and it seems to me that a localised vaso-motor disturbance in the terminal fibres of the vagus in the first part of the duodenum might be the cause of some of the cases of duodenal ulcer. If this vaso-motor theory be correct, it is easy/

easy to understand how the ulcer occurs.

If the vasomotor nerves that run in the nerve trunks of the extremities are liable to disorder of their function as seen in Raynaud's disease, I see no reason why the vasomotor nerves to a viscus should not be liable to a similar derangement, especially as the vessels of the stomach and duodenum have to undergo dilatation and contraction very frequently during the periods of digestion and fasting. If the vasomotor fibres to a region of the pylorus or first portion of the duodenum had their function perturbed it can be easily understood that at some period the mucous membrane, being reduced in its vitality by the anaemia of the contracted vessels, should be attacked by the digestive juices and so an ulcer started, then recurring attacks of ischaemia and congestion similar to that occurring in the fingers in Raynaud's disease would interfere with the proper healing of the part, and so cause the condition known as the chronic peptic ulcer of the duodenum. Of course this theory is purely hypothetical, but it would explain,

- (1) The absence of antecedent pain in duodenal ulcer because a localised contraction of arterioles would not be likely to cause any symptom.
- (2) The progressive character of the ulcer although there be no blood dyscrasia or hypersecretion of gastric hydrochloric acid.

(3)/

- (3) The localisation to the first portion of the duodenum could be explained by this theory in the following manner:

In Raynaud's disease there is a change in the vaso-motor fibres, most frequently of the fingers and toes, i.e. of the terminal fibres of the nerves to the extremities, those fibres that are furthest away from their ganglion cells. In the same way probably the terminal fibres of the vagus (with the vasomotor fibres) run into the first portion of the duodenum, and being most often affected by this perturbation of function, the lesion of the mucous membrane is most often in the area of their distribution. It is interesting to note that 76% chronic gastric ulcers occur in the region of the pylorus, according to Fenwick.

I think it probably, therefore, that vasomotor spasm has some causal relation with chronic duodenal ulcer.

6. A Small Haemorrhage into the wall of the gut would no doubt cause an ulcer to form in many cases, and Fenwick, p.108, gives it as a cause of ulcer of the stomach. In acute ulcers, no doubt, haemorrhages into the mucous or submucous coat, play an important part in their causation. In chronic ulcer, however, their relationship cannot be very close, moreover, there must be some cause for this haemorrhage/

hage if it did give rise to a chronic ulcer, as well as some factor that prevents the ulcer healing; because, as I have pointed out, all artificial ulcers heal rapidly, and haemorrhagic erosions are known to heal. L.Griffini and G. Vassale, quoted by Ewald, Vol.II. p.430, show that such small abrasions are repaired by a formation of genuine peptic glands derived from cells at the margin of the lesion, so leaving no scar in the stomach.

It has been shown, however, that lesions of the central nervous system do cause haemorrhages which lead to ulceration and even perforation of the stomach. Elstein and Schiff both injured the Anterior Corpora Quadrigemina of animals and found that this was followed by haemorrhage and ulceration in the stomach. In discussing these experiments, Ewald Vol.II. p.430, supposes that such a lesion caused a hypersecretion of HCl. which had some bearing upon the formation of the ulcers. Koch and Ewald cut the cervical spinal cord and then easily caused ulceration of the stomach by pouring 5 mille HCl. over the stomachs. These experiments show that lesions of the central nervous system, giving rise to submucous haemorrhage, may have some bearing upon peptic ulceration. In my opinion, it is quite possible that lesions in the region of the corpora quadrigemina may destroy or irritate either the vasomotor centre/

centre or the trophic centre for the stomach or duodenum, and so be at the bottom of some of these obscure ulcers, but I think it is more likely that these vasomotor or trophic fibres are affected, not at their centres, but whilst they run in the nerve (the vagus or sympathetic) probably owing to an endo or perineuritis.

7. Mechanical Injury I do not think has any direct relationship to duodenal ulcer. The stomach contents, by the time they enter the duodenum are reduced to a pulpy states which could not cause an abrasion of the mucous membrane, or if my chance some foreign body did pass into the duodenum and scratch it, the lesion would soon heal up.

External violence seldom affects the duodenum and when it does, the lesion is usually very severe. I can find records of 13 cases of laceration of the duodenum, usually due to severe falls upon the abdomen. Perry & Shaw quote two cases in 18,000 post-mortems and records of nine other cases. One case is recorded as a result of vomiting. J. F. H. Broadbent records two cases, Lancet of 1903, p.1501.

8. Bactericidal Influence has been suggested as a cause of the peptic ulcer. Tubercular, typhoid, anthrax, and probably syphilitic ulceration are undoubtedly/

doubtedly due to organismal infection, and they all occur in the duodenum (Perry & Shap, p.189) but they are rare, and when found do not bear much resemblance to the typical peptic ulcer. A study of an admirable paper by Cushing and Livingood "Contributions to the Science of Medicine" dedicated to W. H. Welch, 1900", shows that bacteria are very uncommon in the stomach and duodenum. In a fasting dog (12 hours after a meal) the stomach yielded no cultures at all.

Duodenum showed 81 colonies.

Jejunum 50 cm. below stomach showed 3 colonies.

"	100	"	"	"	"	174	"
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"	157	"	"	"	was sterile		
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Ileum	247	"	"	"	showed 63 colonies.		
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"	337	"	"	"	"	827	"
---	-----	---	---	---	---	-----	---

"	10 cm. above ileo-caecal valve showed 5000 colonies.					
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Also in cases of stomach and duodenal ulceration, although there is a breach of surface in the intestinal mucous membrane, organisms do not seem to play much part in the extension of the lesion, and unlike any ulcerated surface elsewhere the danger of pyaemia or septicaemia is remote.

It has been urged that many chronic peptic ulcers are really tubercular. This fact is very hard to disprove, because in amny tubercular lesions, e.g. caseous/

caseous glands, it is almost impossible to see the bacilli in sections. Cultures are often not successful and only by inoculating guinea pigs or other animals can the true nature of the lesion be made out. In an ulcer there is not much material to use for inoculating. It might be urged that the bacilli had started the lesion, but the gastric ferments had caused the progress.

Peptic ulcer of the duodenum is undoubtedly often associated with tubercle elsewhere, but the reason for this is, I think, that the general health being below par, owing to the disturbed digestion, the body is liable to the attack of tubercle bacilli in other organs. Boettcher, quoted by Fenwick, has found organisms in the edges of chronic ulcers, but no special type of organism is described.

9. Inflammation of the walls of the Duodenum.

That duodenal ulceration occurs as a sequel to inflammation of the mucous membrane is nearly certain, as I pointed out in discussing the type of ulcer that occurs after burns. And that chronic peptic ulcer may follow an acute inflammation is quite possible if any pathological condition is present to interfere with the natural process of repair. Duodenitis is not an uncommon morbid condition and arises from several/

eral causes. I have referred to its occurrence after burns, in which case it is probably due to a toxin circulating in the blood, which is excreted by the duodenal mucous membrane. Other toxins also are undoubtedly excreted in the same way, and in the process of excretion give rise to irritation of the intestinal mucous membrane; for instance, lead seems to irritate the whole intestinal tract and in lead poisoning there is often an intense enterocolitis set up (Osler, p.1064, Guy & Ferrier, p.576) In chronic Bright's disease also toxins are excreted by the intestinal mucous membrane setting up an enteritis. In such cases if a sub-mucous haemorrhage occurs and gives rise to an acute ulcer, and if the toxins continue to be excreted, such an ulcer would tend to be progressive and assume the characters of a typical peptic ulcer, but there would certainly be evidence of the primary enteritis in the form of probably a small cell infiltration of the walls of the gut, when examined under the microscope. . In Perry & Shaw's investigations, Bright's disease occurred in 7% of all post mortems, but it occurred in 16% of the cases of duodenal ulcer, showing that probably there is some causal relationship between nephritis and ulcer of the duodenum.

An inflammation of the solitary glands might possibly give rise to an ulcer in the duodenum, just as/

as it gives rise to acute ulcer in the stomach and such an ulcer might become progressive, but Perry & Shaw never found the solitary glands in the duodenum inflamed without the lymph follicles of the rest of the intestinal tract being affected as well, so ulcer of the stomach would be more likely to occur than ulcer of the duodenum from this cause.

Haemorrhagic erosions, such as occur in the stomach, also are met with in the duodenum, small rounded ulcers, evidently due to submucous haemorrhages. They are always situated above the bile papilla, and are much less common than in the stomach. Perry & Shaw, p.180, only found ten cases, five of which were associated with heart disease, three with general septic states, and two with granular kidney disease.

Therefore, inflammation in the structures of the duodenal mucous membrane does occur, and at times gives rise to superficial ulceration, but rarely, I think, does it cause the chronic ulcer, which is characterised by the absence of any antecedent symptoms and absence of inflammatory reaction in its immediate neighbourhood.

All the foregoing theories as to the origin of chronic peptic ulcer of the duodenum seem open to objection as a cause of the majority of such ulcers. Therefore/

Therefore, I think, that the following theory may throw some light on the condition, although it is dismissed as improbable by Riegel in Nothnagel's Encyclopoedia (Diseases of the Stomach) as a cause of ulcer of the stomach. It seems to have been first mentioned by Stockton in the Medical News, No.2 1893, but I have been unable to obtain a copy of the original article. Wilks and Moxon in their textbook on Pathology, p.386, state the gastric ulcer is probably due to a nervous influence and has a close analogy to simple ulcer of the cornea, but they do not describe the "simple ulcer of the cornea" or state its pathology.

10. This theory is a neurotrophic one, and suggests that by the influence of some process analogous to Herpes Zoster, idiopathic haematoma auris, or herpetic gangrene, some distinct and persevering nerve perturbation, a localised area of duodenal mucous membrane is rendered below par. It becomes affected by the gastric digestive ferments and an ulcer forms. Such an ulcer would be progressive and not show any great tendency to repair. It would probably be free from inflammatory reaction in the surrounding tissues, and probably would be without antecedent symptoms.

Pathology/

Pathology at the present day, recognises several superficial lesions that result from nerve perturbation; in fact, trophic lesions. In locomotor ataxy the perforating ulcer is characteristic, a localised gangrene, not due to obvious vascular disturbance such as embolism or thrombosis, without inflammatory reaction, except when attacked by extraneous organisms, and the surrounding tissues exhibit a loss of recuperative power.

It is well known that after injury to a nerve of a limb, or in a severe neuritis of such a nerve, the skin gets glossy and atrophic; vesicles, bullae, ulcers and even gangrene occur. In Raynaud's disease, which is distinctly a nerve affection and probably only a special set of fibres are affected, the vasomotor fibres, Munro of Glasgow in 1899, p.190, described in the peripheral nerves areas of parenchymatous degeneration, where only the sheath of Schwann and proliferating nuclei remained. Also in Herpes Zoster, which is another superficial neurotrophic lesion, Head & Campbell in "Brain", XXIII., p.362, found an inflammation of the posterior nerve roots of the nerve affected, with degenerated nerve fibres in the posterior columns of the cord, and degenerated fibres in the peripheral nerve as far as the skin. These facts show that a morbid condition in the nerves will/

will give rise to trophic changes in small areas in their distribution and very often in some special area, as in locomotor, the ulcer under the ball of the great toe, herpes zoster in the peripheral distribution of one of the intercostal nerves, in Raynaud's disease, usually in the fingers and toes (although Raynaud's disease is probably essentially a vasomotor change). Such trophic changes in the nerves to the internal organs seem quite possible to me and multiple intestinal ulcers have been described as occurring after multiple degenerative neuritis, due to infectious diseases by Lorenz & Minkowski, where the ulcers occurred in the jejunum, quoted by Hemmeter, p.623. Acland & Hale White also described trophic ulcers occurring in the intestine in spinal disease (Pathological Transactions, 1885) Another point in favour of this theory is shown in the disease known as Beri Beri. According to Hektwen, p.659, Neuritis of the pneumogastriacs is not uncommon in this disease, and recently Hamilton Wright, M.D. Director of the Institute of Medical Research, Federated Malay States, in a book, "An Inquiry into the Etiology and Pathology of Beri Beri" has shown that a local lesion occurs in the mucous membrane of the duodenum. An inflammation and punctiform haemorrhages and sometimes ulcer occurs. It seems to me that such a condition in the duodenum/

duodenum might probably be due to the neuritis of the vagi. In this connection it is interesting to quote an observation made by Dr Chaytor W. White, in the B.M.J. of 1892, Vol.I., p.1359, where a case of perforating duodenal ulcer is described as occurring in a Mohammedan soldier, aged 24, and Dr Wight states that "Since the occurrence of the above, I find on enquiry that natives of India do suffer frequently from duodenal ulceration from some unaccountably cause." I have been quite unable to find any other data as to the relationship between these cases of ulcer of the duodenum and beri beri.

The Vagi do undoubtedly convey the vasomotor and trophic nerves to the region of the pylorus and first part of the duodenum. Pawlow, p.53. If a neuritis from some cause occurs in the vagi and affected especially the trophic fibres, that would account for many of the hitherto unexplained features of duodenal peptic ulcer. The general causes of neuritis are as follows:

1. Traumatic, which I do not think has any relationship to the lesion under discussion.

2. Toxic, as in chloroform, lead, arsenic, mercury, zinc, copper, and phosphorus poisoning.

It is interesting to note that my cases of "Ellis" had a distinct history of lead poisoning, but against this/

this type of neuritis being a common cause of duodenal ulceration I find that in all the post mortems referred to in the Report on the Arsenical poisoning that occurred through drinking contaminated beer, no case of duodenal ulcer was described.

3. Endogenous toxins, such as diphtheria, scarlet fever, sepsis, malaria, tubercle, all cause a neuritis occasionally.

4. Infectious diseases, such as leprosy and beri beri, cause a neuritis.

5. Cachetic conditions, such as diabetes, rheumatism, gout, cancer, arterio-sclerosis are given by Hektoen as causing neuritis. However, it is found that most of the cases of duodenal ulcer have little relation to the foregoing morbid conditions, But our knowledge of trophic lesions is still imperfect, for none of the foregoing have any very special relationship to herpes zoster or Raynaud's disease.

The arguments in favour of this theory I think are as follows:-

1. Age that duodenal ulcer occurs, in early adult life but may occur in children and even in old age.

2. Sex. That men are more liable, as I have shown, to some of the forms of trophic nerve lesions.

3. Absence of any apparent cause for the ulcer, and/

and absence of symptoms, till the ulcer has reached such a depth that haemorrhage or perforation occurs.

4. The type of the ulcer, almost always in the first portion of the duodenum, almost always single. Absence of inflammation around the ulcer.

5. The fact that such ulceration does not heal readily, as shown by surgeons operating for very chronic gastric disorders and finding such disorder secondary to an old ulcer in the duodenum, and a perfect cure being affected by performing a gastro-jejunosomy and so giving the duodenum absolute rest and probable freedom from the gastric ferments. In these cases I think that the gastric perturbation may either be set up reflexly from the ulcer, or that it be due to the same nerve influence that has given rise to the lesion in the duodenum, but in the stomach the influence not being so marked. In support of this theory my second case is extremely interesting, a man with a three years history of gastric disturbance, and then sudden death from perforation of a duodenal ulcer, which was characteristic in being single and in the first portion. The gastric disturbance was probably secondary to the adhesions around the pylorus giving rise to some dilatation of the stomach and a tendency to attacks of gastritis. On section of this ulcer the base of old/

old organised fibrous tissue is well seen, at the very edge of the ulcer, where the mucous membrane only down to the muscularis mucosae has been digested away, the vessels in the submucous coat are seen to be patent and fairly normal, showing that probably this ulcer had not been due to either embolus or thrombosis. A nerve fibre evidently of Auerbach's plexus is well seen showing evidence of endo and perineuritis. Such a specimen I consider is markedly in favour of a nerve cause for this ulcer. I regret exceedingly that I did not get sections from the vagi and that my specimen had not been more elaborately treated in the first place (by placing and hardening in Muller's fluid) so as to show nerve changes better.

Recently some experiments have been made in connection with this neurotrophic theory by de La Vedora, quoted in Nothnagel's Encyclopoedia, p.569, where injury to the vagi was not followed by any change of the gastric mucous membrane, whilst injury to the sympathetic system, either in the splanchnics, or coeliac plexus caused either erosions or necroses in 41% of the cases, in the region of the pylorus, and in these cases there was also set up a condition of hyperacidity of the gastric juice. Yeran, quoted also by Stockton, in Nothnagels Encyclopoedia, p.570/

p.570, produced invariably gastric ulcer in the stomachs of rabbits by section of the vagi below the diaphragm, similar results being obtained by Saitha (Gaz. Degli Ospedeli, Milan 1900, Vol.XXI., P.599).

These experiments seem to show that the vagi are more probably the path through which trophic influence reaches the stomach and duodenum. I admit, however, that in Pawlow's work, where great numbers of vagotomies had been done in dogs, there is only one record of gastric ulcer developing. And all my arguments would, in the duodenum, apply to a lesion in the sympathetic system, except that the whole duodenum is supplied by the sympathetic system, whilst only the very first portion is supplied by the vagi, and it is in this portion that the great majority of ulcers occur.

It is interesting to follow Pawlow's reasoning as to the cause of the hypersecretion of HCl. in his case of round ulcer in an miniature stomach. In this case the centrally excited secretion in the stomach was normal, showing that the glands, centrifugal nerves, and the corresponding nerve centre in the medulla were normal. When the increased secretion of the second hour was observed, and we know that this secretion is a reflex one, it must be taken to/

to prove that the augmented excitability of the secretory apparatus at this stage has originated either in the centripetal nerves or their nerve endings.

In conclusion, I consider that the majority of typical chronic peptic ulcers of the duodenum are due to some perturbation of the nerve supply to an area of the mucous membrane; such an area is rendered below par and is acted upon by the HCl. and pepsin of the gastric juice, which causes the rounded, terraced, progressive perforating ulcer.

At times a chronic ulcer may undoubtedly follow an acute lesion in the duodenum, such as follows burns, submucous haemorrhages from any cause, vasomotor spasm (which may possibly play a more important role than I have given it), inflammation of the duodenal mucous membrane, haemorrhagic erosions or cysts of Brunner's glands from any cause; but in all these cases, as I pointed out, it is necessary to prevent the ulcer healing as by grave anaemia, or by hyperchlorhydria, so carrying out the essentials given by Ewald that there must be "A failure of the due proportion between the acidity of the gastric juice and the constitution of the blood to cause a peptic ulcer."

In/

In such cases one must suppose that the initial lesion in the duodenum reflexly irritates the nervous mechanism and reflexly gives rise to a hypersecretion of HCl. that keeps up the ulceration.

Process of Repair in Duodenal Ulceration.

Anatomically the duodenal mucous membrane differs from the gastric mucous membrane in several important points:-

1. Absence of rugae or folds at the most frequent site of ulcer. In the fundus of the stomach a comparatively large loss of mucous membrane can be covered in my the lax surrounding tissue, but in the first portion of the duodenum such an area would have to be covered by a new formation of tissue.

2. Presence of Brunner's glands in the sub-mucous coat I think, would rather help repair when compared with the mucous membrane of the pyloric region of the stomach, where there is practically no submucous tissue. In small superficial erosions, such as might occur after superficial haemorrhages or inflammation of the lymph follicles, are readily repaired by a proliferation of the adjacent glands and connective tissue elements. Griffini and Vassale, quoted by Fenwick, p.37, have shown that this occurs in the stomach, and the resulting cicatrix/

atrix is full of new glands. When the lesion is more extensive, however, it heals by the formation of new fibrous tissue following a small cell infiltration of the regions surrounding the ulcer, (in mucous, submucous and muscular coats). This fibrous tissue gradually contracts, so bringing the edges of the ulcer nearer together, and at last there is left a small area of fibrous tissue, not covered by mucous membrane. This, of course, gives rise to some puckering in the wall of the gut. If the ulcer be very large then healing takes place in the same way, but the centre of the cicatrix may remain of low vitality, as the surrounding tissue contracts and so obstructs the vessels. Such a cicatrix will be liable to break down and give rise to fresh attacks of ulceration. Hauser (Nothnagel, p.572) has found that even in large cicatrices gland tubules are found in the edges or even in the centre of the cicatrix. They are probably of an adenomatous nature, and would have a bearing upon the appearance of carcinoma in such a cicatrix at a later date.

Agencies that retard the healing of an ulcer:

If the neurotrophic theory of cause of the ulcer is true, then the reason why such an ulcer does not heal very readily is quite obvious. The cause of the/

the primary lesion is still probably acting and therefore the tissues surrounding the ulcer are deficient in recuperative power.

There are other agencies that interfere with the healing of a chronic ulcer, which I shall now discuss:

1. Gastric hyperchlorhydria is it be present. It still remains to be proved how often this affection complicates an ulcer in the duodenum, Boas, Devie, Roux and Robin having found excess of acid in the stomach contents, whilst Leube and Richmann found subacidity. Hemmeter found the amount of acid normal in two cases and excessive in one. The reason why hyperchlorhydria is sometimes present I have already discussed and when present it undoubtedly would exert an unfavourable influence on the healing of the ulcer.

2. Want of rest is cited by Fenwick as retarding the healing of an ulcer, and undoubtedly in the stomach it may play some part, but in the duodenum even in the first portion, the range of movement is limited by its mesentery, also substances that rub over the surface of the ulcer will not irritate it much mechanically. Acute ulcers are known to heal readily in spite of the movements of the gut.

3. Deficient blood supply is also given by Fenwick/

Fenwick as a retarding agency to the healing of ulcers in the region of the pylorus and duodenum.

Normally the pyloric region does not get as much blood as the fundus, but it is still very vascular and personally I do not think that this normal arrangement has much influence. When the ulcer is extremely chronic, however, there may be set up a condition of endarteritis obliterans in the surrounding blood vessels, which undoubtedly would have an extremely prejudicial effect on the repair of the ulcer.

Local conditions have a marked bearing upon the chronicity of an ulcer.

(1) Adhesions formed between the peritoneum covering the base of the ulcer with the surrounding structures will undoubtedly hinder the contraction that is necessary to approximate the sides of the lesion. This is similar to the ulcer that occurs over the tibia of the leg, where the subjacent bone prevents the necessary contraction of the newly formed reparative tissue.

(2) If the ulcer be of large size, then there will be great difficulty in healing, and when a cicatrix does form, it is apt to narrow the lumen of the gut, giving rise to further symptoms of gastric dilatation.

(3) Fibroid or fatty degeneration of the mucous membrane/

membrane such as occur after middle life (Fenwick, p.130) would affect the healing of an ulcer to some extent in old people.

Constitutional conditions have at times an effect on these ulcers, but they are not always present, and yet the ulcer remains chronic. Therefore they are not the essential reason why duodenal ulcers heal so slowly, but when present they have a prejudicial effect on the ulcer, such conditions as anaemia from any cause, malaria, syphilis, chronic heart disease, chronic nephritis, arterio-fibrosis or Phthisis.

Results of Duodenal Ulceration.

1. Haemorrhage, I will discuss under the symptomatology of the disease.

2. Perforation of the Duodenum. This is an accident that frequently follows ulceration, and in these cases where there is no antecedent history forms the only symptom. The perforation may take place into the general peritoneal cavity, giving rise to general peritonitis, or if there be adhesions the peritonitis may be localised.

1. Acute general peritonitis is a common result of chronic duodenal ulceration. It occurred in 61 out/

out of 124 fatal cases, collected by Fenwick. In Fenwick's acute primary type of ulcer, it occurred in 92% of the cases, of which 86% were ulcers of the anterior wall. Perry & Shaw had 52 cases of perforation in 70 cases of ulcer. Collin, quoted by Hemmeter, has collected 262 cases of perforation. When these figures are compared with the number of cases following ulceration of the stomach, the difference is very great. Fenwick gives $5\frac{1}{2}\%$ gastric ulcers cause general peritonitis, Welch $6\frac{1}{2}\%$ and Brinton 13%. The reasons for this discrepancy are as follows:-

(a) The thin walls of the duodenum when compared with the stomach.

(b) The type of ulcer that is most frequent in the duodenum usually has a minimum of inflammatory reaction, so that protective plastic lymph is not so often thrown out (The duodenum often does become adherent to adjacent structures, however, Fenwick p.31 found traces of adhesions in 42% of his cases of duodenal ulcer).

(c) The high ^{8m}interduodenal pressure may have something to do with this frequency of perforation.

When compared with the frequency of chronic duodenal ulcer, these figures with reference to perforation are misleading, for in the 52 cases of perforation/

perforation collected by Perry & Shaw, p.207, 23 had no previous history of disease. In fact the primary symptom was peritonitis, thus showing that there must be a number of cases of ulcer that never have any symptoms at all. Collin, quoted by Hemmeter, found 39 cases of cicatrices of old duodenal ulceration. Perry & Shaw found evidence of repair in 50% of their cases of ulcer of the duodenum. I consider that this absence of symptoms explains Fenwick's acute primary type of duodenal ulcer, which has probably the same pathogenesis as the chronic peptic ulcer, but has no antecedent symptoms and so inflammatory reaction in the surrounding tissues. Although called an acute ulcer, there is nothing to prove that the ulcer has not been present for a considerable time before the perforation or large haemorrhage.

Symptoms of Ulcer of the Duodenum, as far as they have bearing upon the pathogenesis.

In the peptic type of ulcer the onset and prevalence of the disease until either perforation into the peritoneum or a large haemorrhage occurs, is usually without symptoms at all. Perry & Shaw in 151 cases found no history of abdominal trouble in 91 cases, and they state, "That in many cases the patient had not exposed his duodenum to unusual risk and was in excellent/

excellent health till the onset of either haemorrhage or perforation." Cullen in Scottish Medical and Surgical Journal, July 1897, gives 53% of ulcer with no antecedent history. Fenwick states, however, that 74% of his cases had a history of abdominal disorder before the onset of typical symptoms. Morot states that 20% are latent. The main symptoms are pain, vomiting and haemorrhage.

Pain: This, the most frequent symptom complained of. Fenwick found a history of it in 30 out of 43 cases, Perry and Shaw in 42 out of 60 cases. In character it bears a close resemblance to the pain that occurs in gastric ulcer, but seems not to be felt so often in the back. It is described as either a burning or a gnawing pain, usually felt in the epigastrium a little to the right of the middle line. Hemmeter localises it as at the lower edge of the liver in the right para-sternal line to the right of the pylorus and somewhat below it. Often the pain is described as radiating towards the epigastrium. Kreuz quoted by Hemmeter, states that the pain radiates upwards toward the epigastrium and down toward pelvis, but not to the loins. It must be remembered that pain is often a personal factor, and what in many men is merely discomfort in others is described as agonising.

The/

The relation that the pain of duodenal ulceration bears to the ingestion of food was thought to have some diagnostic significance, but this is not always so. Often the pain is only felt two or three hours after food, and often it is felt worse at night, but not with such regularity as to make it an important diagnostic point. In Perry & Shaw's paper out of the 60 cases only two had the pain at a definite interval after food. Ewald, page 470, states that in at least 90% of the cases it is impossible to state whether the ulcer is in the duodenum or stomach, and gives as diagnostic points that the pains come on some time after eating, and a dull sensitiveness on pressure well to the right of the middle line of in the epigastrium. Why there is so little pain with such a well marked pathological lesion is hard to explain. In the stomach pain is a well marked symptom and was always present in 265 cases collected by Fenwick. I think the explanation is that irritating substances, such as solid lumps of food, etc., are reduced by the stomach to a semi-fluid state, and are then much less irritating. Also the duodenum is less movable than the stomach, and therefore the site of the ulcer is less dragged upon. In my second case there was a three years' history of pain in the region of the umbilicus and it/

it is interesting to note that it usually came on during the early hours of the morning when the stomach was presumably empty. The pain was not increased by taking food. Straining and exertion are described as increasing the pain when it is present.

Vomiting: According to Fenwick, vomiting occurred in 20% of his cases, and had no relation to the taking of food, but he does not state the nature of the vomited matter. It is quite possible, I think, that in duodenal ulcer there is set up a hypersecretion of gastric juice which accumulates in the stomach during the night and then is vomited. Oppenheimer, quoted by Hemmeter, met with vomiting in 17 cases out of 100. Krauss, quoted by the same author, states that vomiting only occurs as a result of the stenosis of the duodenum, or else at the climax of an attack of gastralgia. This shows that vomiting, as well as pain, has not the diagnostic significance in duodenal ulcer that they have in gastric ulcer, and in view of the pathology of the affection, I do not see why vomiting should be characteristic of the affection. An associated chronic catarrh of the stomach may cause vomiting, but such a condition is, I think, an accidental association of two diseases. The relation that hyperchlorhydria bears/

bears to duodenal ulceration I have already discussed. Perry & Shaw found vomiting was a prominent symptom in 20 out of 60 cases. It had no definite relation to food and in one case had lasted for four years. In two cases there was a history of gastric crises, but no other symptom of locomotor ataxy.

Constipation is a usual accompaniment according to Fenwick, but diarrhoea occurred in 8% of his cases. The lesion is situated so high up in the intestinal tract that it does not seem to have much effect upon the movements of the lower bowel. Constipation is of moment with regard to perforation, for as I have pointed out it seems to increase the intra-duodenal pressure, as is seen by the occurrence of duodenal pouches, more often in cases of constipation.

Haemorrhage is the most important medical diagnostic point in regard to duodenal ulceration. From the nature of the affection it is clear that small haemorrhages must occur at a very early period in the formation of the ulcer, but if small it will almost certainly be carried onward by the intestinal peristalsis, being mixed intimately by the influx of the bile and pancreatic juice, then partially or wholly/

wholly digested and so not recognised by the patient in the motions. Even a large haemorrhage that is only partially digested, so that it renders the motions tarry is often overlooked by the patient, especially if there be no pain. I think from the nature of the ulcer and the fixed position of the duodenum that unless a large vessel be opened the haemorrhage will not be very great, because there seems to be nothing to prevent the normal retraction of the coats of the vessel which is such a great factor in the spontaneous arrest of bleeding; also once a thrombosis has formed in the wounded vessel the duodenum, unlike the stomach being nearly fixed and not liable to much movement, there is not much likelihood of it being displaced. Fenwick states that a condition of endarteritis obliterans is a great factor in preventing haemorrhage in chronic ulcers. If a large vessel be opened, the the blood may either regurgitate into the stomach or pass onwards into the intestine. Fenwick states that 40% of chronic duodenal ulcers have a history of marked haemorrhage and in 17 cases seven had melaena alone, five haematemesis alone, and in five cases there was both haematemesis and melaena. Perry & Shaw collected 23 cases, in which nine had haematemesis, nine melaena, and five had both. According to Hemmeter, 1/3 of the cases have haemorrhage which can be recognised/

ised. Of course these percentages of haemorrhage vary with the acumen of the observers, and of the patients, because all the patients I think must have haemorrhage from the ulcer, although it may not be possible to recognise it by ordinary clinical methods, or else no other symptom being present the patient does not come under observation.

When a haemorrhage does occur and is profuse, it points to the fact that the ulcer is on the posterior wall of the gut and therefore not so very liable to set up an acute peritonitis. Fenwick states that in fatal cases of duodenal ulcer, 35% die of an haemorrhage, and in all his fatal haemorrhagic cases the ulcer was on the posterior wall of the gut. It is stated that haemorrhage is more frequent and more profuse in the acute type of ulcers, but the vessels being fairly healthy the haemorrhage usually ceases soon and does not cause death so often as in chronic ulcer, where the bleeding is apt to persist for a long time on account of the diseased state of the vessels and so wear out the patient. However, an examination of my sections shows that the vessels are not much affected, even in the case where there was a three years' history of abdominal pain and thick organised fibrous tissue is to be found external to the serous coat, showing that the ulcer was of considerable duration.

Haemorrhage/

Haemorrhage was the prominent symptom of two of my cases and when melaena occurs in an apparently healthy adult man, without cirrhosis of liver, haemorrhoids, or evidence of tumour of the bowel, the probability is that it is due to an ulcer in the first portion of the duodenum (Fenwick, p.157)

The occurrence of symptoms of functional disease of the stomach, such as heartburn, waterbrash, gaseous eructions, although they do occur as antecedents to the more pronounced symptoms of duodenal ulcer, have no great diagnostic significance.

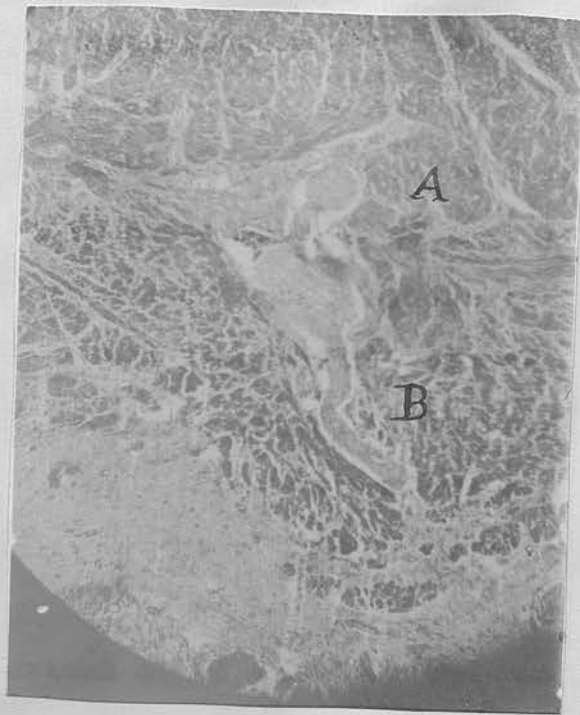
Icterus, such as occurred in my case of the man Ellis, points to a turgescence of the duodenal mucous membrane and when not apparently due to the presence of an obvious cause such as gall stones, is a symptom of duodenitis or a result of stenosis of the gall duct, due to cicatricial contraction of a scar of an old ulcer. It is not of much diagnostic significance.

The symptoms of an ulcer of the duodenum are rather vague, but the signs are much more so. In the great majority of cases there are no signs present. Sometimes thickening may be felt in the region of the pylorus, as in cases of pyloric ulcer, but it is a rare condition. Increase in the epigastric/

gastric superficial reflex may occur as in gastric ulcer, but it does not help much.

Perforation of the gut and general or localised peritonitis I consider is a result of the ulcer and not a symptom.

The following pages are devoted to the details of four cases which have come under my personal observation.



*Microphotograph showing degenerated
nerve fibre. A. In transverse section
B. In longitudinal section.*

Slide II. Y.

C A S E S.CASE I.

Thomas Tindall, aged 28, married, Electric light worker. Admitted February 17th, 1902. Born and brought up in Chester.

Family History:

Father died 69 of apoplexy. Mother alive and well. Three brothers, one died of fever (?); one sister, alive and well.

Social History:

Patient has always had a good home, a steady worker, not a teetotaller, usually had one pint of beer a day. Glass of gin often on Saturday night, plenty of good food. For last six years has worked for electric light company, worked a good deal with red lead. Never been "leaded".

Previous Health:

Usual children's ailments, never had typhoid fever. No accidents. Never suffered from any form of dyspepsia. No pain, vomiting, water brash, etc. Never any trouble with bowels. No history of venereal disease (Wife has two children, no miscarriages, children quite healthy.) No tubercular history and patient was not an "alcoholic".

History/

History of Present Illness:

On February 16th patient had done a hard day's work. Came home, had tea at 6.30 p.m. of ham, bread and tea. No discomfort after it. At 11 p.m. when patient had just got into bed, he was seized with very violent pain in stomach, in region of umbilicus. In about 15 minutes he was sick, but brought up only a little mucus. Pain was agonising, not limited to any single spot. Sent for a doctor who gave him a pill. Eased pain for a little, but patient did not sleep. Next morning pain very severe. No vomiting. No diarrhoea. Doctor saw him at 11 a.m. and advised removal to Chester Infirmary. Came to Infirmary at 4 p.m. in a cab, partially dressed.

State on Admission:

Patient is well developed man, swathy(?) and evidently collapsed. Slight cyanosis. Drawn anxious expression. Not evidently in great pain. Lies in bed with knees drawn up. Pure costal respiration of 50. Pulse cannot be felt at wrist. Heart beating at 144, sounds weak. Temperature 97°F.

Alimentary System:

Tongue furred, dry and brown, no saliva evidently. Abdomen slightly distended, very hard, does not move on/

on respiration. Palpation, abdominal walls extremely rigid and not very much tenderness. Most marked in Right iliac region. No evidence of free fluid in flanks. Percussion. Liver dullness down to margin of ribs. Tympanitic all over abdomen. Note rather higher pitched over right iliac region.

Other systems seemed fairly normal, except that patient had not passed urine since 12 midnight on the 16th. On passing catheter IV. ounces high coloured urine was drawn off, free from albumin.

Diagnosis:

of Staff of Chester Infirmary. Perforating Peritonitis, probably fulminating appendicitis. Immediate operation advised.

Treatment:

The pill given on the night of February 16th was "Pil. opii, Gr. I." On admission I gave the man Strych. Sulph. gr. 1/30, and an enema of VI. oz. beef tea (hot) with one oz. brandy. This was retained. Patient was put to bed with hot water bottles, large 1-30 carbolic fomentation over abdomen and had small bits of ice to suck, on account of the intense thirst. The consultation of the staff was at 5 p.m. and operation took place at 6.45 p.m, Mr Taylor of Chester operating. Immediately before operation the man's pulse/

pulse was fair, 140, and could be felt at the wrist. Temperature 98°F. He was given Strych.Sulph. gr. 1/30, Digitalis Gr. 1/100, and another enema of beeftea and brandy.

Mr Taylor opened in the right semilunar line, and on opening the peritoneum a quantity of thin, brown grumous fluid escaped. The intestines were congested. No free gas in peritoneum. The appendix was found and appeared to be acutely inflamed, so it was removed (on laying it open the walls and interior were normal, only the peritoneum was congested) The patient being too collapsed to stand further operative measures, the peritoneum was washed out with normal saline solution and a large drainage tube passed down into the pelvic pouch of peritoneum. When patient was back in bed no pulse could be felt at the wrist, and breathing was very shallow. 30 m.m. ether was given hypodermically.

Progress:

During night 9 p.m. patient rallied considerably. The dressing over the tube was changed because it was soaked with thin, odourless, and yellowish discharge. At midnight patient passed flatus, had not been sick and stated that he felt "much better". At 2 a.m. there was very severe abdominal pain, so Morph.Sulph. 8 1/6 was given hypodermically. On morning of 18th patient/

patient seemed better. Pulse could be easily felt, 130, and of fair volume. Patient was allowed sips of ice. Passed urine 24 oz. in forenoon and also passed flatus. About midday patient felt very sick, but on retching nothing was vomited. Nausea continued all forenoon and patient complained of tasting and smelling the chloroform. At 4 p.m. I gave patient 4 oz. black coffee on account of the sickness. At 5 p.m. patient was very much collapsed, but nausea had ceased, and pain was not markedly present. By 6 p.m. patient was in extremis, and he died at 8 p.m. Till the coffee was given, patient had nothing except ice by the mouth. He had four saline enemata, $\frac{1}{2}$ pint each.

Section:

From notes in post mortem book of Chester Infirmary, post mortem examination of the abdomen of Thomas Tindall, aged 28 was made by Dr H. G. Carlisle and Dr L. H. Hamilton; diagnosis, "Septic peritonitis"

Body: Well nourished. Operation wound in right iliac region. On opening the abdominal cavity about two pints brownish fluid escaped. A small quantity of recent lymph was found over anterior surface of stomach. On lifting up stomach, omentum and transverse colon, a quantity of fresh yellowish flakes of lymph were noticed in the region of the pylorus/

pylorus. Intestines were congested, especially in region of right iliac fossa. On the anterior wall of first part of duodenum was found perforation about size of crow-quill, with clean cut edges, with considerable quantity of recent plastic lymph in the neighbourhood. On pressing on stomach fluid escaped through the perforation. Stomach and duodenum were removed and opened along the lesser curvature and upper margin. An ulcer of the duodenum was found, the size of a sixpence on anterior and inferior wall of the duodenum, within $\frac{1}{2}$ inch of the pylorus. Stomach and duodenum otherwise healthy. No ulcers to be found in rest of intestine. Liver slightly fatty, kidneys and spleen apparently normal. There was only permission to examine the abdomen.



The specimen was removed and kept in 2% formalin solution. In July 1903 when I decided to take this matter up, I photographed the ulcer (photo A.) This photo shows very well

(a) The smooth surface of the stomach just above the pylorus.

(b) The fold of the pylorus.

(c) The smooth surface of the mucous membrane of the first portion of the duodenum, very similar to the naked eye, to that of the stomach.

(d) The ulcer close up to the pyloric fold, perfectly round and punched out in appearance, with a lens the terracing can be seen in the photo. At the bottom of the ulcer is a round black hole which is the perforation which opens into the general peritoneal cavity. There was an absence of any redness around the ulcer or any obvious trace of inflammatory reaction. Also, to my mind, the ulcer has a naked eye resemblance to a perforating ulcer, such as I have met with under the ball of the great toe in a case of locomotor ataxy and which is a well marked clinical entity. Also on the closest investigation of the actual specimen, and also of the photo I can find no trace of any other pathological lesion.

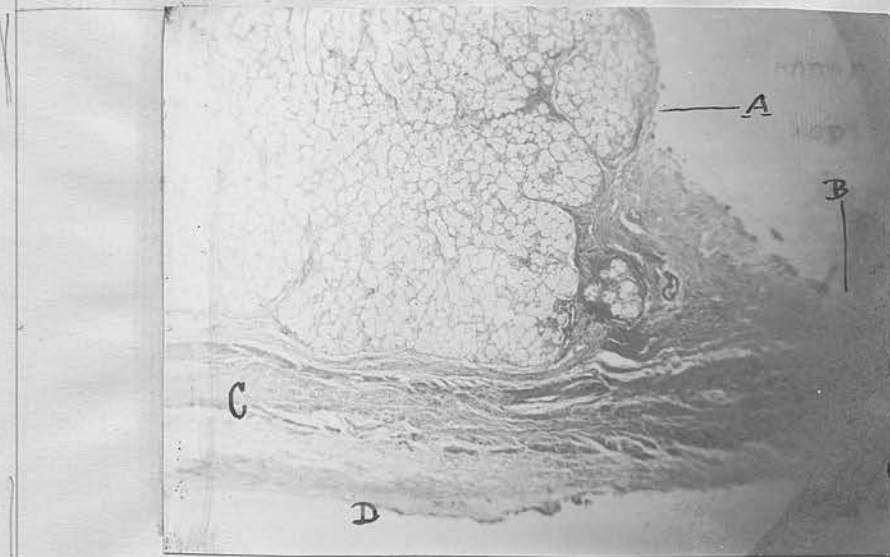
This photo has also been used to show the valvulae conniventes commencing in the second portion of the/

the duodenum and also the papilla of Vater, which is well marked.

Having photographed the specimen, the ulcer was cut out and treated in the following manner.

The stomach and duodenum had been kept for two months in a 2% solution of Formalin in water, so it was thoroughly washed in water and then put into 30% alcohol for 24 hours. Then into 70% alcohol for 24 hours, then 95% alcohol for 24 hours, and then absolute alcohol for two days. Then the specimen was put into a mixture of equal parts of CHCl_3 and $\text{C}_2\text{H}_6\text{O}$ for 24 hours, then into CHCl_3 for 24 hours. Then put into an oven for 12 hours, having added an equal quantity of paraffin to the vessel containing the specimen in chloroform. Then the specimen was transferred to pure paraffin in the oven and kept there for another 24 hours. Having blocked the cooled specimen, the sections were cut with a Richert's microtome. The sections were then floated into albuminised slides, dried, the paraffin dissolved out with Xylol, and the Xylol removed by absolute alcohol. Then 70% alcohol, and then water. Some of the sections were stained with Brazilin and others with haematoxylin. Then they were dehydrated with absolute alcohol, cleared with xylol and mounted in Canada Balsam.

I send with this thesis five of the best slides of each ulcer, three of each stained with haematoxylin and two stained with Brazilin.



- A. Side of ulcer without much inflammatory reaction.
- B. Floor of ulcer formed by muscular layer.
- C. Muscle coat.
- D. Peritoneum.

On examining the slide under the low power, the following points are noted (Slides I, 2, 3, 4, 5, 6.)

(1) That the ulcer has extended down to the muscular coat.

(2) Brunner's glands are well seen and at the sides of the section traces of the muscularis mucosae and fundi of Lieberkuhn's follicles.

(3) Absence of small cell infiltration, either in the muscle or in the gland structures.

(4) The edges give the impression that the parts/

parts that have been lost have been digested away without much injury to the subjacent structures.

(5) In the angle of the ulcer ^{are} is well seen some of the vessels (arterioles and venules) that ramify in the septa of fibrous tissue between the acini of Brunner's glands, and that these vessels are not thrombosed, nor are their walls much thickened, if at all. If this patient had not died from peritonitis and the ulcer had spread a little bit more, I think that this vessel seen in the section must have been eroded, and so haemorrhage taken place, but the surrounding tissues being apparently healthy and the man's blood being normal, not having lost its power of coagulating, spontaneous arrest of that bleeding would probably soon have taken place, and if the haemorrhage had been of small amount it would probably never have been noticed clinically. I can find no trace of nerve structures in any of my slides of this ulcer, probably because I have not happened to cut any of the regions where the nerves were present.

CASE II.

Charles Hughes, aet 23. Single. Farm servant.
Admitted October 6th, 1902. Born in North Wales.
For last three years has worked on a farm at Blacon,
near Chester.

Family History:

Father alive and well. Mother alive and well.
Three brothers, alive and well. One sister, died
"in childbed".

Social History:

Patient has been on a farm all his days, food
good, always lived in fresh air. Not a teetotaler,
gets intoxicated on beer occasionally.

Previous illnesses:

For last three years has "been troubled with his
stomach". Pain during night, seldom during day, and
no relation to food. Much flatulence, sometimes vom-
ited in early morning, never any great quantity - and
usually quite clear stuff, like water. Recently has
been better. No other illnesses of any moment, and
no other gastric symptoms.

History of Present Illness:

On the afternoon of October 4th patient was wash-
ing in the stable, when suddenly seized with very great
pain/

pain in abdomen, chiefly around umbilicus. Had to be carried into the farm, where he was put to bed and turpentine stupes applied to the abdomen. There was no vomiting, nor diarrhoea (bowels had moved naturally on the previous day.) Pain became a little better during the night of October 4th, stupes being applied constantly (One every two hours). Patient had nothing by the mouth, except sips of cold water. Pain continued moderate all through October 5th till about 8 p.m. when vomiting commenced, and pain became very severe again. A doctor was sent for at 10 p.m. who came at 11 p.m. and gave patient a pill, prohibited anything being given by the mouth. Vomiting of brownish fluid continued all through the night, and by next morning there was marked swelling of the abdomen. Doctor came at 11 a.m. and advised immediate removal to the Infirmary.

On admission to the Infirmary, patient was too ill to give any history, and his friends did not seem able to give much information.

State on Admission:

Patient in an almost moribund state. Did not seem to have any pain. Pulse uncountable. Temperature 97.2F., Respirations, 56 and purely thoracic.

Abdomen/

Abdomen:

Was markedly and uniformly distended. The skin in the region of the umbilicus was abraded and markedly discoloured (due to the constant application of turpentine). Regurgitant vomiting was present of dark brown grumous material. Bladder was empty. Patient was too ill to allow a prolonged examination. Heart sounds were normal, but very rapid and faint.

Diagnosis:

Acute peritonitis, probably perforated gastric ulcer. Arrived at an account of the history of dyspepsia.

Treatment:

Patient was given enema of 10 oz. normal saline solution, with 2 oz. brandy. A hypodermic injection of Strych.Sulph. Gr. 1/15.

At 3.15 p.m. Mr Taylor assisted by Mr Hamilton operated under Ch Cl₃.

An incision 4 inches long was made into the linea alba above the umbilicus. On opening the peritoneum free gas escaped. The peritoneum was deeply injected, and contained a considerably quantity of brownish serum. Stomach was found, but on examination no perforation could be found. At this stage of the operation patient collapsed very markedly so/

so the peritoneum was flushed out with normal saline solution. A large drainage tube put into the wound, four stitches introduced through entire thickness of abdominal wall and tied, and patient put back to bed. When in bed 1/100 gr. digitalis was given hypodermically, but patient died at 6 p.m.

Permission to make a post mortem examination of the abdomen alone was allowed, so operation wound was opened up and abdomen examined through it.

Notes from P.M. Book of Chester Infirmary:

Section on body of Charles Hughes, aet 23, October 7th, 1902. Diagnosis, Septic peritonitis.

H. E. Carlisle and L. H. Hamilton.

Peritoneum contained about 4 pints brown fluid, with flakes of recent lymph in it. Intestines and omentum deeply injected and matted together with considerable quantity of recent lymph. On pulling up the stomach it was found that there was a perforation about the size of a pea, on the anterior wall of duodenum, surrounded by recent lymph. The pylorus was closely adherent by fibrous bands to the neck of the gall bladder. A band of fibrous tissue also ran from the first portion of the duodenum to the transverse fissure of the liver. All the parts in the region of the pylorus were deeply matted together and/

and considerable difficulty was experienced in removing the duodenum and pancreas, which were very firmly adherent. On opening the stomach which was enlarged, along the lesser curvature and the duodenum along the upper margin, an ulcer of the first portion of the duodenum was found, situated on the anterior and inferior wall of the first portion, oval in shape with the long axis transverse to the gut. At its lower end it invaded the pyloric ring and at this end there was a perforation about $\frac{1}{2}$ inch in diameter. Floor of the ulcer seemed to be formed of fibrous tissue of the surrounding adhesions. Stomach was dilated, but otherwise normal. Intestines showed no evidence of other ulceration. Liver slightly fatty, kidneys slightly fatty. The base of the ulcer was formed by fibrous tissue, evidently of fairly old growth, because it seemed quite organised into connective tissue.



↑
Duodenum & Bile Papilla. Oval Ulcer

↑
Dilated Stomach.

On the accompanying photo the ulcer is well shown, running slightly obliquely. It also shows well the pyloric ring, how it seems to project into the lumen of the duodenum like the cervix uteri into the vagina. Also the atrium of the stomach is well shown, devoid of rugae. The bile papilla is to be seen and the large valvulae conniventes commencing above the level of the papilla of Vater. This specimen does not show the anatomy or other points nearly so well as photo of Case I.

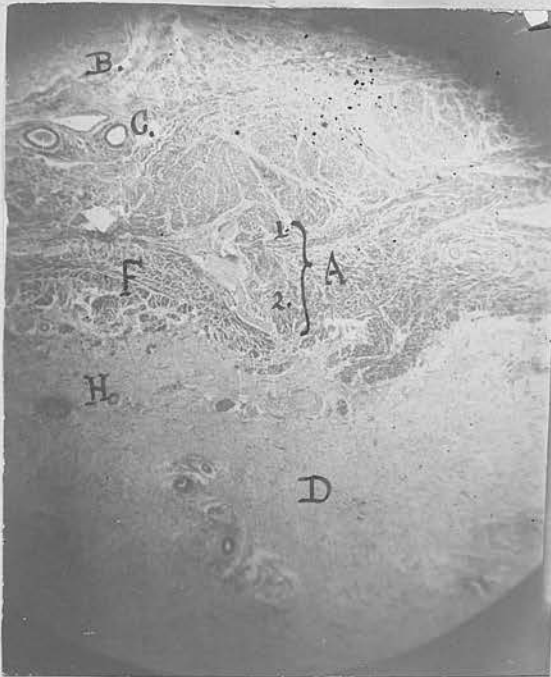
After photographing the specimen, the ulcer was cut out and a portion of the edge treated exactly as in Case I. and sections were taken of the very edge of the ulcer, in the hope of demonstrating any degenerated nerve fibres or changes in the blood vessels.

On examining the section under the low power it looks as if the glands of Brunner were next the lumen of the gut, but the fibres of the muscularis mucosae can be seen quite clearly with the lower portions of the glands of Lieberkuhn, but what impresses me most is the fact that there is no inflammatory reaction, no small cell infiltration, etc., although on the peritoneal side there is evidence of thick organised lymph, showing that the condition must/

must have persisted for a very considerable time. I consider that this points to a necrobiosis due to the digestive ferments, and not to a sloughing of the superficial portions of the mucous membrane. Also the superficial cells stain badly, showing probably their protoplasm and nuclei and "below par". The muscular coat is seen to be arranged in layers, and does not show much evidence of inflammatory reaction. The contained vessels, both in the muscular coat and in the septa between Brunner's glands seem fairly normal. At all events, they are not markedly atheromatous, but in the section II. X which is stained with Brazilin, there is beautifully shown a nerve fibre, both in longitudinal and cross section (Vide Photo and slide), which shows I consider, marked endoneuritis, where there is excess of connective tissue between the bundles of nerve fibrils.

After examining all my sections most carefully, I have chosen the best for this thesis. They all show well the various changes in the mucous membrane, the fairly healthy blood vessels, and the one specially marked shows best the nerve degeneration.

This case, to me, is most interesting. A young, fairly healthy man, probably with hyperchlorhydria for/



- A. Nerve fibre.
 1. Transverse Section.
 2. Longitudinal Section.
- B. Gland of Brunner.
- C. Healthy blood vessel.
- D. Organised fibrous tissue
 External to peritoneum
 (an old adhesion)
- F. Muscular Tunic.
- H. Level of Peritoneum.

for three years, then sudden death, due to the ulcer in his duodenum. The cause of the ulcer, I consider, to be nerve degeneration, either in the terminal filaments of the vagus, where the lower neuron is affected at its cell either in the pons or near the Anterior Corpora Quadrigemina (vide Ewald's Experiments) in the sympathetic fibres springing from the fifth thoracic nerve and downwards, and as these two great systems meet in the first portion of the duodenum, where their plexuses intermingle, it is impossible to say which is affected, but probably the vagus or why does the lesion almost always occur so near the pylorus?

CASE III.

Ann Tweedie, aet 22, single. Housemaid.

Admitted 4th January, 1903. Born and brought up at Sealand, Cheshire.

Family History:

Father alive and well. Mother alive and well. One brother, aet 31, alive and well.

Social History:

Very good. Father is a small farmer, so patient has always had good home and food.

Previous Illnesses:

Typhoid fever four years ago. No shortness of breath, nor history of anaemia. No dyspepsia or any symptom of it. Menstruation commenced at 14 and regular. Patient suffers from constipation. Before onset of present illness patient was not in the least anaemic.

History of Present Illness:

On the morning of January 4th, 1903, before breakfast, whilst patient was standing on a chair and putting a box on a high shelf, she felt a sudden pain in pit of stomach, as if something had given way. Pain only lasted a few seconds, and patient got down off/

off chair. In a few minutes she felt very faint so had to lie down. She was not sick at all, nor did she had any hausea at first. Then patient fainted. When she recovered her senses she was in bed. She had been unconscious about three quarters of an hour. Dr Giffen, of Chester, had been called in, who found patient in a faint, very pale (She usually had very pronounced colour), very feeble rapid pulse and sighing respiration. He gave her 1/30 strych.Sulph. hypodermically. Dr Giffen diagnosed internal haemorrhage, and sent patient in a cart to Chester Infirmary.

State on Admission:

Patient lies flat on her back, in a semi-conscious state, blanched and pinched features, shallow and sighing respiration. Pulse 140. Temperature 97°F. Respiration 38.

Alimentary System:

No tympanites, no evidence of tenderness over stomach or other part of abdomen. Liver dullness is down to lower margin of ribs. Nothing abnormal to be felt in pelvis. Abdominal walls quite lax, no fulness in pelvis, or iliac fossae.

Circulatory System:

Nothing abnormal to be noted.

Respiratory/

Respiratory System:

Nothing abnormal to be noted.

Urinary System:

Nothing abnormal to be noted.

Physical examination was negative in all the systems. From this short description it is evident that patient is suffering from shock, and probably internal haemorrhage, and it is of interest that there was no vomiting at all, nor any swelling to be felt either over the pancreas or in the pelvis.

Progress and Treatment:

During the first day patient was not allowed anything by the mouth. On admission Strych.Sulph. gr. 1/30 was given hypodermically and at 2 p.m. and 8 p.m. saline enemata of $\frac{1}{2}$ pint were given. Patient was much better in the evening, experienced no pain, but felt very faint if she raised her head at all. Passed comfortable night.

January 5th: Seemed much better in the morning, but very blanched. At 10 a.m. a saline enema was given, which moved the bowels. At first an ordinary motion, then a large quantity, about 2 pints, tarry black motion, then one pint of fluid clotted red blood, which at once suggested the true nature of the/

the case. Patient fainted whilst in bed in the afternoon, but soon rallied. No nausea and no pain. During the night patient had $1/6$ gr. morphine sulphate, because she was restless. Also nutrient enemata ordered every six hours. (Their composition varied.)

January 6th: This morning patient felt better. Rectum was washed out by a cleansing enema and a large quantity of tarry stool came away. On microscopical examination numerous crenated red blood corpuscles were seen.

Further Progress:

Patient had no more haemorrhage from the bowel. She got absolutely no drugs whilst she was lying in bed. Rectal feeding and drinking was used for nine days absolutely, patient's mouth being washed every three hours with listerin in solution. After the 9th day water was first allowed by the mouth, then peptonised milk, in 2 oz. feeds every three hours, till the 14th day. After milk and barley water or lime water was used till the end of the 28 days, when Benger's food, etc., were given. Patient got up on February 16th, 1903 for the first time. Left hospital quite well for Parkgate Convalescent Home on March 3rd, and I regret has since been lost sight of, her father at Sealand having died.

This case is peculiar in several ways.

(1) Sudden onset in an apparently perfectly healthy young woman.

(2) Extreme collapse.

(3) For the first 24 hours no diagnosis was made. Perforated gastric ulcer, Ectopic gestation, Deitle's crisis, were each suggested by members of the Infirmary staff; but at first the patient was so desperately ill that nothing would be done but watch her.

The points which point to the condition being one of duodenal ulceration are:

1. Sudden onset with no haematemesis whatever.
2. The very large quantity of blood passed per rectum.
3. That some of the blood should be partially digested and take 24 hours before it was passed per rectum, I think shows that the bleeding occurred high up in the intestine.
4. No antecedent history of dyspepsia is most interesting.

I think that gastric ulcer could not have caused the condition or else, with such a large haemorrhage, there would have been vomiting. A tubercular ulcer in the small intestine might possibly cause such a big haemorrhage, but the patient was not tubercular, nor ever had any other tubercular manifestation. The other causes of large intestinal haemorrhage (malignant disease, etc.) hardly could hold in a patient/

patient aged 22. Moreover the recovery with dieting alone was absolute.

Therefore, I consider this case to have been one of a peptic ulcer on the posterior and inner wall of the duodenum, and probably in the first portion, which had opened into a fairly large vessel, causing such a quantity of haemorrhage.

During the first 12 hours that this patient was under my charge an absolute diagnosis, I think, was not possible, although the patient was almost "in extremis". With regard to the treatment, I almost think that she was kept rather long on nutrient enemata, which prolonged the convalescence; and I do not see how bland substances could injure a duodenal ulcer, after they have been partially digested in the stomach and then passed on it a pulpy state. But it must be remembered that anything by the mouth will cause an excretion of HCl. and pepsin which, as I think I proved, is the actual cause of the ulcer spreading, and if nothing be given per os, then the chances of repair are increased, because no HCl. is secreted. But it is very difficult to introduce enough nourishment by the rectum alone, and from observations I have made in cases of gastric ulcer, when rectal feeding is kept up for over 10 days, the convalescence is often very prolonged. Also both in gastric and duodenal ulcer, bread is one of the/

the last things I ever give to patients following the advice of Mr James Taylor, F.R.C.S. of Chester, and I think with good reason; for in Pawlow's tables dieting a dog with round ulcer of the stomach an excessive secretion was poured out on the bread.

Also during convalescence recently I have recommended Cod liver oil early, for the same author has shown that oily substances do not excite the secretion of HCl. and pepsin to any great extent (P.104)

With regard to the cause of the ulcer in this particular case, I am afraid we must theorise. Embolus or thrombosis are both unlikely, there being no vascular lesion, nor blood dyscrasia. The patient's age is against vascular degeneration, and I consider that these cases are only to be explained by some nerve theory, but whether vasomotor spasm of vessels in the duodenum, or an inhibited trophic influence of some small area, it is impossible to say. Of course, there were no other signs of nerve degeneration or perversion, but in Herpes Zoster no other nerve lesion is present at the time of the eruption as a rule. The usual causes of peripheral neuritis in this case were absent, (1) Traumatic; (2) Toxic, i.e. CHCl_3 , $\text{C}_2\text{H}_5\text{O}_6$, Lead, Arsenic, Mercury, Zinc, Phosphorus, or the endogenous poisons of diphtheria, Scarlet/

Scarlet Fever, Typhoid, and the curious toxins accompanying rheumatism, gout, diabetes, or malaria.

This neurotrophic theory suggests that by the influence of some process analogous to herpes, to idiopathic haematoma auris, to Raynaud's disease, or to herpetic gangrene, some distinct and persevering nerve perturbation, we may best explain the recognised and unaccounted for features of the clinical history of such a case.

CASE IV.

Joseph Ellis, wood machinist. Born at New Ferry, Residing at Neston.

Social Conditions:

Patient has always been a good workman, so always had plenty of good food and a good home.

Family History:

Father, 72, quite well. Mother, 70, quite well. Brothers, four, alive and well. Sisters, four, alive and well.

Previous Illnesses:

Scarlet fever and measles as a boy. No other illnesses till patient was 36. About three years ago patient was overworked and commenced to have pain after taking food. Pain situated just above umbilicus, also a considerable amount of flatulence. About one month after patient first noticed the pain he commenced to vomit, at first only occasionally, and later once every 24 hours. The vomiting occurred almost always at night, about 3 a.m. About this time patient continued at his work and was quite well during the day, but every night about 3 a.m. he awoke with great pain in the pit of stomach, which was relieved by vomiting. His wife described the/

the vomit as exactly like whey. There was never any solid food in it. Patient at this time suffered from marked constipation. This state of things continued for two months, when patient went to his doctor in Newferry, who put him to bed for two weeks on a milk and bread diet. At the end of the fortnight patient was still the same, nocturnal pain and vomiting, fairly well during the day, with marked constipation. About four months from the beginning of the illness patient changed his dietary, lived entirely off albuminous materials (lean meat, eggs, fish, and no toast or bread). Within a fortnight the pain and vomiting had ceased entirely, and the constipation became much better.

Since March 1901 patient has never had any illness, taken an ordinary dietary, never had any pain, flatulence or vomiting.

I think from this description of the patient, who is an extremely well read and intelligent man, that he suffered from hyperchlorhydria, brought on by irregular meals, and possibly a duodenal ulcer three years ago.

History of Present Illness:

On Tuesday, November 3rd, patient spent the whole day (10 hours) in mixing up red lead, white lead/

lead, oil and tarry rope, using his hands to "wash up" the lead like dough (patient had never worked in lead before.) On the Wednesday patient woke up feeling very seedy, but no definite pains, went and worked at the lead for two or three hours, and then used it for filling up some joints in the workshop.

On November 5th, when patient woke up, he felt ill, pain in forehead and nausea. Bowels did not move, and wife noticed that patient was puffy under the eyelids, and was slightly jaundiced. (Patient usually has a very high - pink and white - colour). He went to work during the afternoon. On November 6th patient had to stay in bed. Throbbing, intense headache, no appetite, marked constipation, (only relieved by a "double strong" seidlitz powder.) Hands and feet became very cold and wax-like for several hours. No pain in abdomen.

On November 7th patient was much worse. Headache, which was by far the most prominent symptom, was described as maddening. No appetite, no vomiting or pain in body. Colour very slightly jaundiced, otherwise good. My colleague, Dr Grant of Parkgate, saw Mr Ellis on Saturday afternoon and diagnosed "lead poisoning", put patient on milk diet with a mixture containing sulphate of magnesia every four hours.

On/

On November 8th I saw Mr Ellis and found he had not slept during the night on account of the headache, which he described as terrible, and not relieved by the medicine. Temperature was 98°F., pulse 90, rather high tension. No abdominal symptoms, no vomiting. Appetite was nil. Colour was slightly yellow, conjunctivae also injected and yellowish. Gums showed a slightly blue line. Tongue furred with a white fur, but quite moist. Bowels moved by the medicine, but motions were composed of small hard scybala. On November 9th patient was much the same, headache a little easier. On November 10th however, there was a very marked change. Whilst patient was lying in bed he fainted about 10 a.m. By midday I saw him; he was very collapsed, semi-conscious, pulse of 135, temperature 97°F. Face was blanched and pinched. I gave him some strychnine and brandy by the mouth. About 4 p.m. when I saw patient again the bowels had just moved and very large quantity of tarry stool was passed, followed by about $\frac{1}{2}$ pint clotted blood. Whilst I was present patient vomited (for the first time) about $\frac{1}{2}$ pint blood and was very collapsed, losing consciousness on the slightest movement. Pulse at the wrist could not be felt. Respiration was sighing and very shallow. Patient was put on a nutrient enemata with/

with small doses of Liq. Morph. Nun. by the mouth. On Thursday, November 11th, patient was much the same - extremely ill, semi-conscious. At 1 p.m. bowels moved, more tarry stool, but no red clots. At 6 p.m. slight haematemesis. At 3 a.m. on November 12th there was another haemorrhage from the bowel, which was the last. Patient by this time seemed "in articulo mortis", but with the aid of saline enemata and strychnine he managed to rally a little. By the end of a week he was much better, quite conscious, but fainted occasionally. Pulse running about 115. No temperature and is being nourished entirely by the rectum. No headache or any other pain. Since the collapse on November 10th, the headache has gone altogether, and there never has been any other pain. This patient got quite well in about three months, and at the present moment has just got back to an ordinary diet, with special instruction not to eat much bread, and has gone away for a change. He intends starting work in the beginning of March, 1904.

I think this case of Mr Ellis is most interesting.

1st. He has a history which looks very much as if there had been a condition of excess of HCl. in the stomach three years ago.

2nd: /

2nd: An attack of acute plumbism with, as its most marked feature, the encephalgia and also probably some duodenitis, accounting for the jaundice - which however, was very slight.

3rd: The marked haemorrhage, which was so severe that it was thought that the patient was certainly going to die.

4th: Absolutely no symptom to point to any affection within the abdomen before the haemorrhage.

Of course at first the question of typhoid was thought of, but Widal's test, as done by the Pathological Laboratory in Liverpool, was negative. This case, like that of Ann Tweedie, seems to me to have been one of a duodenal ulcer is the posterior wall, opening into some big vessel. How long the ulcer had been there it is impossible to say, may be from the time of the former illness (three years ago), or it might be an example of the acute type, and the direct cause being the lead poisoning, causing either a haemorrhage in the duodenum, which was eaten into the HCl. and pepsin; or else a neuritis of the duodenal nerves giving rise to an area where the vitality was lowered, so opening the door to an attack by digestive ferments, lead being such a well marked nerve poison.

This/

This case also in the history seems to support the mode of treating hyperchlorhydria by an albuminous diet. My cases III. & IV. show that ulcers on the posterior wall of the duodenum do heal. A case published in the Lancet on May 11th, 1895, by Marmaduke Shield, is of interest when a man aged 23 died from septic peritonitis following a duodenal ulcer on the anterior wall. There was a history of duodenal ulcer several years previously and the scar was found on the posterior wall of the duodenum. And if in these cases no large vessel had been encountered, it is quite possible that the ulcer might have run its course, quite unknown to the patient, till cicatricial stenosis of the duodenum or some other remote sequel had supervened.

On April 4th Mr Ellis was at work in Parkgate, perfectly well and quite free from any symptom of dyspepsia. He has gained $1\frac{1}{2}$ stone in weight during the last three months. I think this proves that the haemorrhage could not have come from any malignant ulceration.